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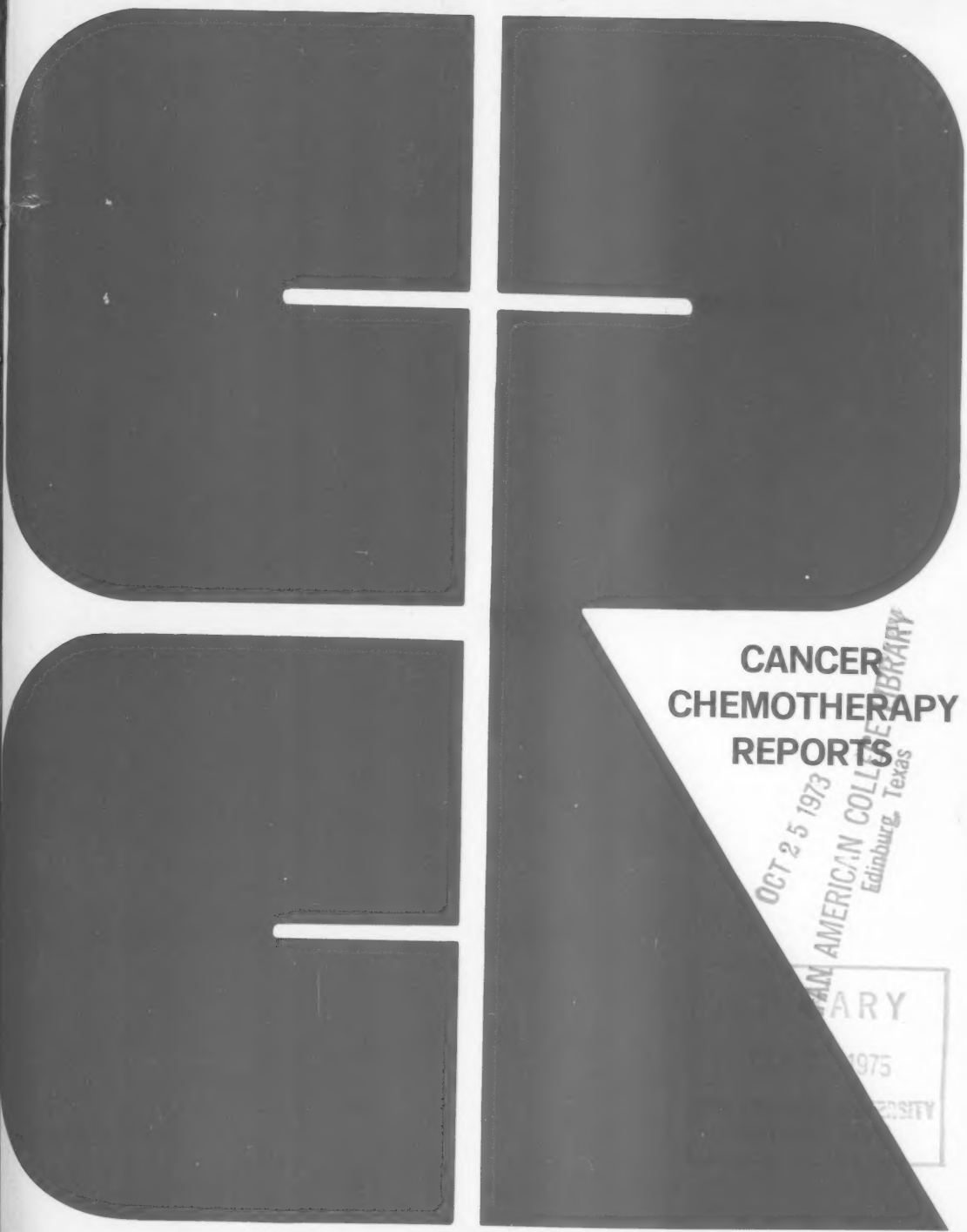

CANCER CHEMOTHERAPY REPORTS

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Part 3

March 1973
Vol. 4, No. 2

Cancer Chemotherapy Reports

National Cancer Institute

Frank J. Rauscher, Jr., *Director*

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1st International Workshop for Therapy of Lung Cancer

Division of Cancer Treatment
National Cancer Institute

Oleg S. Selawry and Aron Primack, editors

Airlie, Virginia

October 16–20, 1972

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The Secretary of Health, Education, and Welfare has determined that the publication of this periodical is necessary in the transaction of the public business required by law of this Department. Use of funds for printing this periodical has been approved by the Director of the Office of Management and Budget through November 30, 1973.

Guest Editors' Introduction

Bronchogenic carcinoma is the leading cause of death from cancer in an increasing number of countries. Therapeutic end results are only slowly improving, yet important leads for improved therapy are at hand.

The 1st International Workshop for Therapy of Lung Cancer was held at Airlie House, Airlie, Virginia, USA, October 16–20, 1972, to facilitate intensive exchange by invited experts. The conference was sponsored by the National Cancer Institute of the United States in cooperation with the International Union Against Cancer.

Selected papers from this conference are presented. The cooperation of the editors of *Cancer Chemotherapy Reports*, permitting publication in one issue of the Journal, is gratefully acknowledged.
The opinions and thoughts expressed by the individual authors are not necessarily those of the guest editors or the Journal.

Oleg S. Selawry, M.D.

Aron Primack, M.D.

Introduction to Proceedings

C. Gordon Zubrod [1]

Dr. Frank Rauscher, our Director, sends his regrets that he is unable to be here with you to open this meeting, but extends his thanks for all your hard work. On my part, I welcome you to the 1st International Workshop for Therapy of Lung Cancer. I wish to say how grateful the Institute is, and to add my own gratitude for the time and trouble you have taken to come to this meeting and discuss the problems that exist in the treatment of lung cancer.

We all recognize that the control of lung cancer is one of the greatest challenges that faces us. The new Cancer Act has given great impetus to intensified activities in many fields, but particularly with respect to lung cancer. The Institute currently has a task force on lung cancer. Its activities, however, have concentrated on the problems of tobacco and a safe cigarette. A few years ago our Division of Cancer Treatment decided it was time to have a workshop for developing improvements in the treatment of lung cancer. As many of you know, we have already had several meetings with Dr. Selawry as the head of this working party. The decision was made to get all the interested investigators together to work in small groups and define recommendations on every part of the therapy of lung cancer. Dr. Selawry and his staff have worked mightily to bring this about and I want to thank them for all their hard work. I am sure that the Workshop will be highly productive and will affect our concepts of treatment for years to come.

[1] Director, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

Introduction to the 1st International Workshop for Therapy of Lung Cancer

Oleg S. Selawry [1]

To date, the medical profession still finds it difficult to associate the word "therapy" with the words "lung cancer," with the possible exception of resectable bronchogenic carcinoma. This attitude is understandable: the median survival of all patients, from diagnosis to death, remains less than 6 months and the 5-year survival rate remains less than 10% in major and national surveys. What, then, led to this 1st International Workshop for Therapy of Lung Cancer? First, our mutual awareness of the task at hand; second, our knowledge of important leads which might enable us to improve substantially the therapeutic end results over the next 5–10 years; and third, the realization that progress is facilitated by rapid exchange of information, by coordination of effort, and by cooperation in the conduct of controlled clinical trials.

The task at hand is obvious. Bronchogenic carcinoma is the most commonly lethal cancer in an increasing number of countries. In the United States, we expect 68,800 persons to die of lung cancer in 1972. This amounts to one of every five cancer deaths. For men, one of every three cancer deaths, or more than the combined death rate from the four next most lethal types of cancer (prostate, colon, pancreas, and stomach), will come from lung cancer (1) (table 1). The death rate in the United States is midway between countries such as Scotland, which is at the upper end of the scale, and Mexico, which is at the lower end (2). In the 15 countries represented at this meeting, more than a quarter of a million persons will die of lung cancer this year.

Leads for improvement will be presented in the Keynote Addresses and will be discussed extensively throughout the meeting. Thus, I shall highlight only a few of these. The World Health Organization presented us with a clinically meaningful morphologic classification of four major types of lung cancer (3), each with distinct characteristics of natural history and of therapeutic response.

No progress has been made over the past 25 years toward earlier *diagnosis* of lung cancer. Cytologic examination, in conjunction with fiberoptic bronchoscopy, permits early diagnosis (4), implies segmental or subsegmental origin for most bronchogenic carcinomas (5,6), and thus might further improve the chances for curative surgery.

Technologic and conceptual advances improve the chances for increased local cell kill or eradication of local tumor by the *radiotherapist*, especially for small cell (oat cell) carcinoma (7,8).

Small cell carcinoma is highly sensitive to *chemotherapy* with single agents and combinations of drugs (9). Substantial improvement of survival also appears within reach for adenocarcinoma and large cell carcinoma (10).

Staging is the basis for therapy and for evaluation of response not only for the surgeon, but also for the radiotherapist, chemotherapist, and immunotherapist. Progress in this field will be presented in a subsequent paper.

Immunology provides important prognostic and therapeutic leads.

Biostatistics become increasingly important for study design and stratification of patients, based on quantitation of prognostic factors.

Some crucial gaps of knowledge could be readily closed. Major shortcomings of clinical staging could be unearthed by retrospective and prospective analysis of autopsy findings in patients who die shortly after staging, for example, within 1 month after surgery. The paucity of published data is surprising.

Quantitation of tumor cell load at initiation

[1] National Cancer Institute-Veterans' Administration Medical Oncology Service, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

of therapy and quantitation of response are inexact. An increasing number of tumor-related marker substances such as isoenzymes and peptide hormones offer opportunities for better quantitation. In addition, cell kinetic studies will enable us to define the pool of actively dividing cells before and at certain times after initiation of therapy. Assays for determination of colony forming tumor cells are within reach for quantitation of proportionate cell kill as a result of therapy. More than ten new antineoplastic drugs become available each year. Many currently used drugs are insufficiently evaluated. To be exact, only six of 30 presently used drugs were tested in 14 or more patients with cancers from each of the four major cell types (9). Studies of combination therapy using different drugs and combination therapy using different modalities of treatment were mostly empirical. Moreover, such combination therapies were not adapted to the characteristics of specific types of bronchogenic carcinoma. Important leads from preclinical systems offer increasing rationale for clinical studies.

For the deliberations of this Workshop, it is suggested that we focus on current data, that we define the next immediate steps deemed necessary, and that we explore optimal ways to improve therapy, in cooperation with existing organizations.

TABLE 1.—Estimated cancer deaths during 1972 in the United States: six most common sites (1)

Site	Estimated No. of deaths		
	Both sexes	Men	Women
Lung	68,800	55,800	13,000
Colon	36,500	16,900	19,600
Breast	32,250	250	32,000
Pancreas	18,800	10,700	8,100
Prostate	17,600	17,600	0
Stomach	15,100	9,000	6,100
All sites	345,000	187,000	158,000

The sentiments expressed in this introduction are best summarized in the words of one of the pioneers in the field of lung cancer therapy, the late David Karnofsky:

> "It is essential to progress that we intensify our attack on this disease and study all possible methods that may contribute to its control. From the patients' point of view, in most instances, it is desirable to maintain an aggressive therapeutic approach" (11).

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Welcome From the Veterans' Administration

Lyndon E. Lee [1]

The Veterans' Administration is a part of the general United States health care system involving both the professional government and the public. Public Law 89–785, which was passed in November 1966, indicates that the VA is a part of the community and is to share with and be shared by the community. This is one fundamental principle upon which we conduct our various cooperative clinical studies. I would like to comment on these controlled, cooperative, goal-directed clinical studies which are carried out within the VA and its many affiliate professional organizations.

The reports presented at this Workshop will help explain principles under which these complicated, costly, and essential programs are carried on. The VA is sometimes credited with initiating the cooperative-group technique. This is not so. Cooperative efforts and goal-directed programs have long been a technique in engineering. They are the basis of much of industrial programs and progress. Within the government, the development of atomic energy and the "man-on-the-moon" project are results of these kinds of collaborative endeavors.

In medicine, the oldest of the cooperative studies of which I am aware was initiated in 1928 by the National Academy of Sciences and the National Research Council under their Committee on Problems of Drug Addiction. It later became the NRC Committee on Drug Addiction and Narcotics, and it is now the Committee on Problems of Drug Abuse, a very forceful, contributory group. In 1928, 1929, and the early 1930s, the pioneers were Dr. William Charles White, Dr. Lyndon Small, and Dr. Nathan Eddy. The latter, at 81, is exceedingly active as a coordinator of these various programs and others for the World Health Organization.

In the VA, under Dr. John Barnwell in the very early 1950s, the VA Cooperative Study on Chemotherapy of Tuberculosis was initiated, with cooperation from the Armed Forces. These two government agencies made a very great contribution in their joint effort in the clinical field, initiating modern approaches to the treatment of tuberculosis.

In the VA, our planned attack on lung cancer began in 1957, in recognition of the increasing incidence and the ghastly toll of this disease. Each year we see in the VA approximately 86,000 patients with cancer. This figure has remained constant since 1965, but the VA incidence of lung cancer has gradually increased since that time. In 1965, 11,210 cases of carcinoma of the bronchus and lung were entered; 3 years later, there were 1000 more cases, for a total of 12,212, and in 1971 there were another 1100 cases, for a total of 13,336. In each year 75% of these were new cases, which gives you an idea of the rate at which these patients die.

In our studies our first concern was early diagnosis. In 1963 the American Cancer Society/VA collaborative study on the screening of potential lung cancer victims was started. We screened 14,000 individuals who were not patients but were residents in our old soldiers' homes. They were asymptomatic. These 14,000 men were subjected every 6 months to a stereo roentgenogram of the chest, a cytologic review of the sputum, and a smoking history in accordance with the guidelines of the American Cancer Society. The study continued for 2 years, ie, 4 screenings per patient. We lost 2000 of the 14,000 men to followup during that review. In 1964 Dr. Abraham Lilienfeld published the results of that study which indicated that of 12,000 men who were over 45 years of age and were screened at 6-month intervals for 2 years, 76 carcinomas of the lung were found. More importantly, 575 of these individuals showed abnormal cytologic findings which were not cancer, including such things as proliferative hyperplasias, dysplasia, metaplasias, and dysker-

[1] Veterans' Administration Central Office, Washington, DC.

ioses. We are now going back to find not only these patients but others who had suspicious roentgenographic findings (1000 in all), and we are attempting to determine the fate of these people 10 years after the time of the study. This was a study of diagnosis.

Our approach to studies on early therapy began with Dr. John Steele in 1963 when we put together clinical material from 100 VA and military hospitals in order to find individuals who had an asymptomatic solitary pulmonary nodule which had been resected. We accumulated data on 1000 cases. Of those 1000 patients, approximately 33% had malignant tumors, among which 55% of the patients over 50 years of age had cancer. The last surviving 93 of these individuals have been followed in the last year thanks to the efforts of Dr. George Higgins. The results of this followup study, which will be published, indicate that early diagnosis and resection of an asymptomatic solitary pulmonary nodule does not change the dismal prognosis in carcinoma of the lung.

Another cooperative group is the VA Surgical Adjuvant Cancer Chemotherapy and Radiotherapy Study Group, now under the chairmanship of Dr. George Higgins. The group pooling data in a uniform manner on these cases includes 23 VA hospitals where resections of lung tumors are carried out in the hope of cures.

Dr. Higgins' group was the first to show the strongly suggestive evidence of the superiority of cyclophosphamide as a surgical adjuvant over placebo for small cell carcinoma of the lung.[2] The group has provided many other specific surgical and adjuvant treatments of lung cancer.

In the VA there is a Pathology Panel which has been studying core material from the various cooperative programs and the results of the VA adjuvant surgical study. This panel is under the chairmanship of Dr. Raymond Yesner. He, Dr. Bruno Gerstl, and Dr. Oscar Auerbach have been our Pathology Panel not only in these studies but in others which I shall mention. Their studies have proven that it is essential in these various programs to have collateral supporting studies (such as mutually agreeable histologic studies) and uniformity in histologic interpretation.

The fourth study which we in the VA have had under way, in addition to early screening and diagnosis, early treatment of nodules, and surgical treatment and resection in lung cancer patients, is a study on incurable cases. This study, under the chairmanship of Dr. Julius Wolf, is the VA Cooperative Cancer Chemotherapy Lung Study Group. This group now includes investigators from 22 hospitals, and was the first major proponent for the use of survival as a criterion for therapeutic response. It was the first group to define major differences in therapeutic responses to specific alkylating agents, showing the superiority of mechlorethamine over cyclophosphamide for epidermoid bronchogenic carcinoma and the superiority of cyclophosphamide over mechlorethamine for small cell anaplastic carcinoma.[3]

Dr. Auerbach, working with these VA cooperative studies, was the first to define the incidence of lung cancer in heavy smokers who died without clinical evidence of cancer, and the first to define the incidence of a second primary carcinoma of the lung in patients who did die of lung cancer.

The National Cancer Institute and the VA have collaborated at our VA Hospital in Washington, DC, in a joint effort to advance multidisciplinary therapeutic treatment by cell type. This effort includes the clinical pharmacologic screening of various drugs from the beginning of chemical synthesis through the early clinical trials. We are continuing and intensifying these collaborative efforts of the VA and the NCI in cooperation with the scientific community here and abroad. This cooperation is a full demonstration of the spirit of Public Law 89–785 which indicates that the VA is a community facility to share with and be shared by the community.

We look forward to this important meeting on lung cancer and to continuing collaboration with participants in this group.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan.

[3] Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard.

Welcome From the International Union Against Cancer (UICC)

R. Flamant [1]

At the 1966 meeting of the International Union Against Cancer (UICC), held in Tokyo, it was decided to establish a Committee on Controlled Therapeutic Trials within the framework of the Commission on Clinical Oncology. This Committee of ten members has been working since 1967 under the chairmanship of Professor D. Schwartz (Villejuif, France). The membership of the Committee was altered after the 1970 meeting of the UICC, which was held in Houston.[2]

It is not the purpose of the Committee to undertake therapeutic trials; its aims can be defined as follows:

1. To study problems concerning the methodology of controlled clinical trials and to promote methodologic development.
2. To facilitate the international exchange of information on controlled clinical trials.
3. To facilitate attempts to coordinate surveys on an international basis.

Methodology of Controlled Clinical Trials and Methodologic Development

It is with this aim in mind that the members of the Committee have been chosen from different disciplines: medical oncologists, surgeons, radiotherapists, and biostatisticians. An important part of the annual meetings of the Committee is devoted to scientific discussions of various problems concerning the methodology of trials. A symposium organized under the aegis of the UICC and held in Villejuif, France, in September 1969, was attended by 11 biostatisticians and eight physicians who reviewed the current trends in the design of therapeutic trials (1,2).

Facilitating the International Exchange of Information on Controlled Clinical Trials

Until recently this problem did not arise on an international level but only within the United States, since almost all the trials were carried out in this country. Within the past few years, as an increasing number of trials have been initiated in Europe, Scandinavia, Japan, the USSR, and other countries, this problem has become of international interest.

It is clearly difficult to conduct controlled clinical trials, and especially comparative ones, according to strict statistical principles, since a study of this type often monopolizes most of the activity of a cooperative study group for several years. Under these circumstances, it is needless to say that before embarking on a trial, a cooperative group, and much more so an individual research worker, will need to be provided with information as accurate as possible concerning the work in progress or in planning elsewhere. Thus, investigators will be able to avoid overlapping and will benefit by the experience of others, including negative results which are not always published. It might even be possible to find partners who can be joined to carry out the work more rapidly.

In 1967 the Committee on Controlled Therapeutic Trials established an Information Office in an attempt to meet this need for information on unpublished trials. Recently, the Cancer Section of the World Health Organization has become interested in this work and has granted half the financial support needed in 1972. The other half has been granted by the UICC. So far, the Office has limited its activities to comparative trials (ie, phase III trials, and phase II trials in which randomization was used, which is more and more frequently the case). The Office has three basic functions:

[1] Executive Secretary, Committee on Controlled Therapeutic Trials, UICC, Villejuif, France.

[2] Membership of the Committee (1970-1974): Prof. D. Schwartz, Chairman (France), Prof. P. Armitage (United Kingdom), Dr. R. Flamant (France), Dr. A. M. Garin (USSR), Prof. E. A. Gehan (US), Dr. J. L. Hayward (United Kingdom), Dr. G. A. Higgins (US), Dr. J. F. Holland (US), Dr. K. Magnus (Norway), and Dr. R. Saracci (Italy).

the collection, registration, and dissemination of information.

Collection of information on controlled clinical trials.—This is done by the members of the Information Office with the support of a network of "corresponding members" representing 26 countries (*see* Appendix 1). A registration form must be completed for each new trial, and the protocol of the trial is attached to this form whenever possible (*see* Appendix 2). The task of collecting information is not equally apportioned among all members of the Office. It is, for instance, particularly heavy for American trials; on the average, there are 18 new trials per year in the United States, which accounts for 42% of all registered trials. Dr. George Higgins, Chief of the Surgical Service, Veterans' Administration Hospital, Washington, DC, has been in charge of this job since 1967.

Registration of information.—Once they are completed by the members of the Office or the corresponding members, the forms are sent to the secretariat of the Information Office in Villejuif, France. The trials are then reviewed. Those meeting the basic statistical requirements established by the Committee are recorded and filed. The files are classified according to the localization of tumors. Within the headings so defined they are further classified according to the treatments to be compared. Lastly, in order to followup the progress of registered trials, we write to those responsible for them every year. Thus, we know the results of some of the trials; occasionally we learn that some trials have been abandoned and the reasons for this decision are defined. Our purpose is to obtain a picture as accurate as possible of all the trials in progress throughout the world at any time. As of October 4, 1972, for instance, the register contained 318 trials in progress or being planned. We can also determine the "incidence" of the trials over a period of time, and appreciate the importance of the work done according to the localization of the tumors and according to the country carrying out the study.

Dissemination of information.—There are two possible ways to disseminate information:

(*a*) Upon request: The Information Office answers directly all requests for information on the registered trials providing those responsible have authorized such information to be given. Mention should be made, in particular, of a request sent by a number of radiotherapists which resulted in the publication of a list of the trials involving radiation therapy registered at the Office (3). The Office has received 123 requests for information since March 1968, 23 of which have been received since March 1972.

(*b*) Systematically: The Information Office publishes a list of all trials registered at the Office. The first list was published in 1969 (4), and the second was published in 1970 (5). The third list has recently been published (6) and is included in a booklet containing a short summary of the methodology of clinical trials. It presents three new items when compared to the first two lists: references to publications concerning some trials which were in the first and second lists and are now completed; for each trial, the name and address of the individual (chairman, coordinator, or secretary) to whom requests for detailed information should be sent; and a separate list of the trials in solid tumors in children. Although these data are probably not exhaustive, I hope their quality will increase in the future, especially because of an increased cooperation with Dr. William Hammond's office.

Facilitating Attempts to Coordinate Surveys on an International Basis

This ambition becomes possible for the first time on the occasion of the present Workshop. This is why the Committee is so pleased that such a meeting can be held, and we thank the National Cancer Institute for its financial and

organizational support. Having had several preparatory sessions for this Workshop with Dr. Oleg Selawry and Dr. Heine Hansen, I can say with what extreme care and sense of efficacy they have prepared this Workshop. I do hope that it will prove a great success and will serve as a model for other organ-related conferences.

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APPENDIX 1.—INFORMATION OFFICE MEMBERSHIP

A. Members of the Office

Belgium	Dr. Kenis	Japan	Dr. Koyama
Federated Republic of Germany	Prof. Wagner	Norway	Dr. Høst
		United Kingdom	Dr. Hayward
France	Dr. Flamant	US	Dr. Higgins
Italy	Dr. Saracci	USSR	Dr. Garin

B. Corresponding Members

Australia	Prof. Loewenthal	Israel	Dr. Steinitz
Austria	Dr. Karrer	Mexico	Dr. Garcia Sainz
Brazil	Dr. Da Silva Neto	New Zealand	Dr. Clarke
Bulgaria	Dr. Kirov	Nigeria	Dr. Ajayi
Canada	Dr. Miller	Poland	Dr. Skolyszewski
Colombia	Dr. Gaitan-Yanguas	Romania	Dr. Costachel
Czechoslovakia	Dr. Cerny	South Africa	Dr. Falkson
Denmark	Dr. Johansen		Dr. Helman
Finland	Dr. Holsti	Sweden	Dr. de Schryver
Germany (Democratic Republic)	Dr. Berndt	Switzerland	Dr. Brunner
		Tunisia	Dr. Mourali
Hungary	Dr. Eckhardt	UAR	Prof. Nasr
Iceland	Dr. Bjarnason	Uganda	Dr. Ziegler
India	Dr. Jussawala	Yugoslavia	Dr. Maricic

APPENDIX 2.—INFORMATION OFFICE ON CONTROLLED THERAPEUTIC TRIALS IN CANCER:

Information required for the registration of trials*

Protocol number:

Purpose of the trial:

Description of disease and patients (TNM):

Description of compared groups, including control group (specify type of surgery, radiotherapy, chemotherapy, doses, methods of administration, etc)

Is the trial carried out by a cooperative group? _____ yes _____ no

If so, what is the name of the group:

Number and names of the participating centers:

Name of the chairman of the trial:

Name of the coordinator of the trial:

Name of the secretary of the trial:

Name and address of the person to whom requests for further information concerning the trial should be sent:

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*This form is to be completed for each trial, the results of which have not yet been published.

Method used for the allocation of patients to treatment groups:

–table of random numbers: _____ _____
yes no

–other (specify):

Time of the allocation of patients to treatment groups:

Necessary number of patients to be entered into the trial:

Date of inclusion of the first patient:

Probable duration of the trial:

Inclusion of patients: _____

Followup: _____

TOTAL: _____

Protocol attached (protocol should be attached whenever possible): _____ _____
yes no

Is permission granted to the Information Office to include this trial in the list which it publishes yearly?† _____ _____
yes no

Is permission granted to the Information Office to publish, together with the list mentioned above, the name and address of the person to whom requests for detailed information concerning this trial should be sent? _____ _____
yes no

If not, is permission granted to the Information Office to give this name and address to those who may apply to the Office for further information concerning this trial? _____ _____
yes no

Remarks:

†Information to be included in this list shall be submitted for approval before the list is sent to the editor.

Name of the person having completed the form:

Signature:

Date:

Completed form to be returned to the secretariat of the Information Office:

R. Flamant, M.D.
Institut Gustave Roussy
16bis, Avenue Paul-Vaillant-Couturier
94, Villejuif (France)

Keynote Address on Pathology of Lung Cancer

Mary J. Matthews [1]

The role of the pathologist in an effective and meaningful lung cancer therapy program is diverse. In his service obligations, the pathologist must diagnose surgical and cytologic specimens of all grades of excellence, of all sizes, and from many sites. He must, sometimes painfully, reexamine his diagnoses at autopsy. In his role as an investigator, he must search to understand the etiology, pathogenesis, morphogenesis, biologic behavior, and ultrastructural characteristics of lung tumors. In his role as co-partner in a project such as this, he must expand or diminish his own well-defined concepts of a disease process to accommodate the definitions of his coworkers, so that instead of speaking as an individual in his diagnoses, he speaks in consonance with many other voices.

With this in mind, Professor Kreyberg and other eminent pathologists contributed a profound service to clinicians and pathologists alike in the development of the World Health Organization (WHO) Histological Classification of Lung Tumors, published in 1967 (1). The classification is intellectually appealing in many areas and is particularly excellent in its precise definition of each of its major categories. It is possibly limited in that it fails to distinguish well-differentiated from poorly differentiated tumors, inferring that the biologic behavior of the two are alike. It is somewhat difficult to understand the separation of carcinoid tumors from bronchial gland tumors, or verrucal squamous cell bronchial lesions from the epidermoid malignancies. Finally, the multiplicity of choices of diagnostic terms would seem to compound the pathologists' difficulties in speaking with one voice and would also seem to create a burden to the clinicians and statisticians.

The attention of the Pathology Panel will be specifically focused on the classification of lung tumors. The classification that is finally approved for use in this project will be made compatible not only with the WHO classification but also with the classification of lung tumors used by the Veterans' Administration Lung Cancer Study Group (2) so that comparability of data can be assured. Because we are aware of the difficulties involved in the diagnosis of lung tumors, especially when using materials obtained from extrapulmonary sites (such as bone, liver, lymph nodes, and brain), we will attempt to improve the reliability of diagnosis particularly in the poorly differentiated, apparently undifferentiated, and anaplastic tumors which in their primary sites may have unquestionable diagnostic features.

The morphogenesis of lung cancer, its induction and modification in the experimental animal model, and the implications of this modification in future lung cancer therapy will be discussed. Premalignant and malignant changes identified in cytologic and surgical specimens have intrigued and plagued the pathologist for decades. The induction of these changes in experimental animal models is exciting. When such changes from premalignant to in situ to frankly infiltrating malignant lesions can be followed by cytologic examination alone over a prolonged time interval in high-risk patients, grave ethical and therapeutic questions may be raised. Beyond this, such data should provide us with much information concerning carcinogenic agents, host response, time required for induction of such tumors, and expected duration of each phase. Cytologic examination may also serve as an indicator of therapeutic response and recrudescent disease, and, possibly, in the premalignant and in situ malignant states it may become a mechanism by which arrest of the neoplastic process can be observed through the use of relatively harmless agents, such as vitamin A.

In vivo cell kinetic studies of patients with lung cancer provide another chronologic di-

[1] National Cancer Institute-Veterans' Administration Medical Oncology Service, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

mension into and understanding of the lifespan and behavior of tumors of different cell types, and these studies may provide a clinical estimation of the duration of disease.

Because cytologic studies offer the most hopeful method of early diagnosis and therapy of lung cancer, the Pathology Panel will also discuss the reliability and variability of cytologic diagnoses, including not only false positives and false negatives, but how precisely diagnoses can be made according to cell type. It is considered feasible that cytologic diagnosis will become acceptable in some cases for definitive therapeutic measures.

The effects of chemotherapy and radiotherapy on target tumors and susceptible host tissues are of considerable concern to the pathologist. Toxic effects of individual chemotherapeutic agents are predictable based on animal toxicity studies. The cumulative or synergistic effects of multiple chemotherapeutic agents are more difficult to assess, particularly in patients who may have co-existing pulmonary, hepatic, hematologic, or renal disease. The success of irradiation in ablating pulmonary tumors is recognized. The subsequent alteration of pulmonary morphology and function in a lung compromised by emphysema and fibrosis is a source of consternation to the radiotherapist and pathologist alike. Evaluation and definition of these changes will be discussed.

Other topics that will be discussed in the Pathology Panel include the adequacy of current staging procedures for lung cancer and the existence of predictable early sites of metastases in different cell types which would guide the clinician in this staging process. The literature contains little beyond generalizations concerning these questions. We will discuss the techniques that can be developed to identify these metastases rapidly, effectively, and inexpensively, so that prompt surgery can be offered to those with localized disease and more appropriate radiotherapy or chemotherapy can be offered to those with unresectable local or extensive disease. A retrospective review of the records of over 200 patients who were considered to have localized disease, who received surgical treatment, and who died within a 30-day postoperative period, for whatever reason, has been undertaken. It was thought that such a review might afford a preliminary evaluation and insight into the adequacy of current staging procedures and the early metastatic behavior of tumors of different cell types. It is anticipated that prospective rather than retrospective studies will provide more valid and meaningful results.

Protocols that have been devised and mechanisms of review of all cytologic, surgical, and postmortem material will be examined and evaluated.

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Keynote Address on Diagnosis, Staging, and Criteria of Response to Therapy for Lung Cancer

David T. Carr [1]

In the preceding address, Dr. Matthews very wisely emphasized the great importance in recognizing the various cell types of bronchogenic carcinoma in any consideration of that disease. In fact, it is more correct to speak of "those diseases," since there can be no doubt that when we are talking about pulmonary cancer we are talking about a wide variety of diseases and we should not think of them as a single entity.

The Panels on Diagnosis, Staging, and Criteria of Response will consider the problem of staging or classification of the anatomic extent of these diseases. In treating each patient the determination of the extent of disease spread is perhaps as important as the determination of cell type. I need not remind you of the great variety of classifications that have been published throughout the years. There have been some that are simple and describe the disease as localized, regional, and disseminated. There have been others that are so complex and difficult to comprehend that probably very few people other than the author have understood what the system is really about.

The American Joint Committee on Cancer Staging and End Results Reporting, a Joint Committee established by the National Cancer Institute, the American Cancer Society, and several other organizations vitally concerned with the cancer problem, has established a task force of people particularly interested in lung cancer. That group took the responsibility of trying to develop a staging system that might be used by people interested in lung cancer, particularly in the United States. The group collected data on more than 2000 patients who had been found to have lung cancer. The cases were followed and data on the survival time and the extent of the cancer at the time of diagnosis were accumulated. More than 100 items of information were abstracted from the records of each patient and all the data were stored in a computer that was programmed to print out survival curves of those patients with any one characteristic or any combination of characteristics. Using these data, a staging system is being developed which is a modification of the TNM system of the TNM Committee of the International Union Against Cancer. The preliminary results obtained by the task force and a tentative TNM classification system will be published in the near future.

The Panels on Diagnosis, Staging, and Criteria of Response to Therapy will also deal with the measurement of response to therapy, because unless we can have some uniform measures of response each of us may be talking about different kinds of good results and may not be communicating.

In addition, during this workshop the Panels will discuss certain aspects of the diagnosis of lung cancer.

[1] Division of Thoracic Disease and Internal Medicine, Mayo Clinic, Rochester, Minn.

Keynote Address on Surgery in the Therapy for Lung Cancer: Surgical Prospects and Priorities for Clinical Research

Clifton F. Mountain [1,2]

SUMMARY

Lung cancer is beyond the scope of surgical cure in 85%–90% of all cases at the time of initial diagnosis. Various adjunctive therapies have failed to improve long-term survival, but improved theoretical understanding and the introduction of chemotherapeutic agents active against solid tumors encourage continued investigations. In such studies, special care should be taken to define terms, to describe the clinical extent of the disease in a standardized manner, and to stratify all trials by the histologic pattern of disease. Discrete types of lung cancer can be identified and our knowledge of their biologic behavior can be used in optimizing our investigations and in assigning priorities to research.

[Cancer Chemother Rep Part 3, vol 4:19–24, 1973]

The contributions of surgery in the management of bronchogenic carcinoma are reasonably well known. Clearly, surgical resection can cure lung cancer. In some classifications of squamous cell carcinoma more than 50% of the patients whose tumors are resected will survive more than 5 years. Yet, in spite of modest improvement in survival rates, we continue to be faced with the therapeutic dilemma that only 7%–8% of all patients will survive their disease.

The overall problem, from the surgical viewpoint, is relatively straightforward: too few patients are diagnosed during a stage of their disease where they meet the criteria of resectability for potential "cure." In reviewing the general world experience, approximately 50 of every 100 patients diagnosed will be selected for thoracotomy. Fifteen of these will undergo surgery for diagnosis only, five will undergo a deliberately palliative resection, and the remaining 30 will undergo resection with some hope of long-term survival. Seven or eight patients, of the total group, will win the battle and three will die in the attempt. In centers for special studies in oncology, the number of patients undergoing surgery without resection will be smaller, the resection rate will be greater, the operative mortality rate will decrease, and the survival will be slightly improved. The effectiveness of surgery is, however, surprisingly uniform among surgeons, assuming a reasonable degree of competence, and it is probably the least significant variable in survival.

The fact must be faced that this disease is

[1] Thoracic Surgical Service, Department of Surgery, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

[2] As chairman of the Committee on Surgery of the Working Party on Lung Cancer, I wish to acknowledge my appreciation and indebtedness to its members (Dr. George Higgins, Washington, DC; Dr. Spencer Payne, Rochester, Minn [Vice-Chairman]; Dr. Herbert Ransdall, Louisville, Ky; and Dr. Ronald Vincent, Buffalo, NY). A number of the concepts presented in this paper represent a distillation of several pleasant and meaningful discussions of the Committee over the past year.

beyond the scope of *surgical* cure in 85%–90% of all cases at the time of initial diagnosis. In our own experience with over 1000 explorations, at the time of surgery 54% of the patients had extension of the disease to the hilar nodes and 35% had extension to the mediastinal nodes. The parietal pleura was involved in 15% and there was direct chest wall invasion in 6%. The mediastinum was invaded in 9% and major vessel invasion occurred in 7%. It is estimated that more than half the patients who have resections for "cure" have unrecognized distal metastases in liver, bone, brain, adrenals, contralateral lung, or kidney at the time of surgery. We became particularly aware of this type of evaluative error during our studies with preoperative irradiation. During the 8–10-week interval between diagnosis and scheduled surgery, a significant number of patients manifested evidence of obvious distal metastatic spread.

Thus, as we review the nature and general dimensions of the therapeutic problem in bronchogenic carcinoma it seems obvious that we must alter our concepts of the traditional role of surgery in this disease if we are to realize any significant improvement in end results. We must recognize lung cancer as essentially a systemic disease at diagnosis. Sometimes it is limited to regional involvement but rarely is it localized to the parenchyma of the lung. Therefore, if survival is to be favorably altered, some type of regional and/or systemic therapy must be utilized as an adjunct to surgery. The potential of this type of therapeutic approach has been widely recognized in principle (1–3), and considerable initial effort has been expended over a number of years in the Adjunctive Chemotherapy Studies of the Veterans' Administration (4,5), the Cooperative University Group (6,7), the National Cooperative Studies of Preoperative Supravoltage Irradiation (8), and by numerous other investigators. In recent reviews of the subject (9,10), it is unfortunately apparent that none of the large controlled studies have demonstrated improvement in long-term survival. Nevertheless, I personally remain optimistic especially in view of recent therapeutic developments.

The concept of employing adjuncts to surgery has now developed a strong and rational theoretical basis. In light of current understandings, particularly with respect to theories of cell population kinetic behavior, we probably could predict failure of earlier clinical experiments. The evidence that a constant fraction of cells is destroyed by a given treatment, regardless of the number of cells present at the time treatment is initiated (11), has major implications for surgical adjunctive therapy. Our personal experience with surgical adjunctive polychemotherapy in drug sensitive sarcomas (9) has been encouraging and may serve as a useful clinical model.

I am persuaded that the causes of failure can be largely understood, new approaches can be designed, and problems can be overcome. Our esteemed friend and colleague at this Conference, Dr. George Higgins, said it very well in an editorial in the *Annals of Thoracic Surgery* (12): "The paucity of positive results should not be particularly surprising. In the first place, this shotgun attack has been directed largely at the extreme periphery of the problem instead of the heart of the matter, the molecular biology of the cancer cell. Secondly, in the impatient tempo of getting results yesterday, it is easy to forget that the effort is still in its infancy. Overly optimistic predictions of an imminent major breakthrough in the cancer field has [sic] raised unwarranted expectations, with a resultant defeatist attitude in some quarters. Failure thus far in no way alters the magnitude of the problem. Efforts must continue at an increasing pace."

Where do we start in our renewed effort and what strategy can be utilized to optimize our game plan?

COMMUNICATIONS

The very depth and scope of our scientific understandings relate to our ability to communicate our observations. Yet the literature is confusing and replete with information which we cannot relate to the data bank of our own experiences. Unfounded differences of opinion, misunderstandings, and results which cannot be duplicated by others are frequently the outcome. This is a long-standing problem which we must, however imperfectly, resolve. Terms

should be defined and subsets in the population should be reliably identified for specific therapeutic trial.

RESEARCH DESIGNS

Studies must be designed and invariably stratified by stage of disease and histologic pattern to reduce variance. The structure of the research effort should permit rapid answers, and we should make every effort to use all currently available knowledge to optimize future approaches. Some index of patient "cost" and risk should be assigned to each adjunct. This index should include a ratio between time of patient involvement and expected survival, morbidity and its discomfort, and mortality. Thus, each adjunctive modality can be evaluated in terms of the current survival experience and the quality of that survival. Therapeutic adjuncts tested in patients with surgically favorable disease should be especially easy to administer and exceptionally safe, with relative freedom from side effects. The demand for such conditions would be progressively less rigid in passing from stage I to stage III disease.

To illustrate the problems of definitions, consider the surgeon's use of "curative resection." Since recurrent disease develops in 75% of the patients undergoing definitive surgery, perhaps the term "reductive surgery" would be more appropriate. The term "definitive reductive surgery" could be applied to resections with the highest expectation for survival. The term "regional reductive surgery" would refer to grossly complete resections in patients where there is a high probability of residual disease. "Adjunctive reductive surgery" would refer to resections in which the major mass of primary tumor and its regional spread is extirpated to the furthest technical extent possible with the certain knowledge that viable tumor remains. These groups would be distinguished from a "palliative surgery" group, in which surgery is undertaken to relieve or prevent intolerable symptoms and thereby improve the quality of life.

The *intent* of the surgeon is important in judging results and I am persuaded that it should be documented in the surgical record. Another problem in definitions relates to "descriptive accuracy." There is considerable difference of opinion as to the results of therapy for superior sulcus tumors. These differences appear to relate to the resectability rate after preoperative irradiation. In examining the literature in an effort to understand these differences, it becomes apparent that the experience with therapy for this type of cancer cannot be pooled since histologic proof of diagnosis is not uniformly required. Most importantly, no distinction is made between (*a*) simple apical tumor, (*b*) tumors associated with "painful apical syndrome," and (*c*) tumors associated with a true "Pancoast's syndrome." Clearly, these distinctions must be made in any definitive study of the problem.

The need to stratify all studies by cell type and anatomic extent of disease should be stressed. Survival experience with respect to these variables and a system of classification and staging have been presented. We must learn to relate our experience to more homogeneous groups if we are to extract its real meaning. The rates of thoracotomy, resection, lymph node involvement, and survival are significantly different between cell types. The behavior of undifferentiated small cell (oat cell) carcinoma is completely different from other cell types; even what clinically appears to be "early" is biologically "late," and independent research approaches are required. Surgery is not justified in this disease since the surgical mortality rate exceeds the surgical survival rate.

Utilizing the results of recent investigations, I would now propose to identify discrete sets in the population of lung cancer patients, and, as a basis for discussion and consideration, I will presume to suggest certain priorities for investigations (table 1).

Occult carcinoma of the lung is clearly not a surgical disease. This interesting type of cancer is being encountered with increasing frequency due to improved techniques in exfoliative cytologic diagnosis and the applications of electron microscopy in cytology. With the introduction of the flexible fiberoptic bronchoscope and techniques of brush biopsy, it has attracted special interest for its diagnostic and evaluative challenges. It should be noted that once the site of origin of the primary lesion is proven, such

TABLE 1.—Lung cancer: investigational therapeutic scheme for squamous cell carcinoma, adenocarcinoma, and large cell carcinoma

Stage	Classification	Estimated frequency*	Survival at 18 mos ± SE (%)	Comment	Therapy priorities†			
					Surgery	Radiation therapy	Chemotherapy	Immunotherapy
0	$T_xN_oM_o$	<1%	Unknown	Occult carcinoma	3	2	Definitive, phase III	1
I	$T_1N_oM_o$	7%	65±4	Adjunctive clinical trial awaits demonstration of effective, safe, and relatively simple adjunctive therapy	Definitive	NW	NW	NW
	$T_2N_oM_o$	18%	53±3		Definitive	NW	NW	NW
	$T_1N_1M_o$	1%	47±10		Definitive	NW	2	1
II	$T_2N_1M_o$	6%	35±5	Strong arguments for adjunctive therapy. High competition for cases. Rationale for radiation therapy priority assumes error of assessing N	Definitive	2, postoperative	1, postoperative	3
III	$T_1N_{2.1}M_o$	½%	ID‡	Surgery can encompass disease	Definitive	1	2	3
	$T_2N_{2.1}M_o$	3%	Est 18%					
	$T_1N_{2.2}M_o$ $T_1N_{2.3}M_o$ $T_2N_{2.2}M_o$ $T_2N_{2.3}M_o$	Unknown	Unknown, est 10%	Surgery cannot encompass disease	3	Definitive	1	2
	$T_{3.1}$any N M_o	0.4%	Est 25%	Superior sulcus tumors potentially resectable	1	Definitive	NW	NW
	$T_{3.2}$any N M_o	10%	Est 16%	Potentially amenable to reductive surgery	2	Definitive	1	3
	$T_{4.2}$any N M_o	10%	11±3	Surgery not well tolerated	NW	Definitive	1	2
	Any M_1	33%	6±4	Disseminated disease, limited trials of reductive surgery might be considered	3	1	Definitive	2
	Mediastinal compression syndrome	2%	4±2	Clinical emergencies	NW	Definitive	1	2
	Oat cell carcinoma	12%	9±1	Clinical behavior of all classifications is similar	NW	Definitive	Definitive	1

*Frequency among all cancer patients.
†1 = first choice for adjunctive therapy; 2 = second choice; 3 = third choice. NW = not warranted.
‡ID = incomplete data.

cases become stage I disease. In true occult carcinoma, however, it would seem that investigational therapeutic strategies should involve immunotherapy and chemotherapy as first priorities. The possible therapeutic role of vitamin A in such cases may prove a valid avenue for study.

Stage I carcinoma has an estimated frequency of 26%. A definite survival gradient can be seen between the T_1 N_0 M_0 lesions and the T_1 N_1 M_0 lesions. In these cases, as in stage II disease, surgical resection is clearly the definitive form of therapy. In my opinion, large-scale cooperative clinical trials in stage I disease should await demonstration of an effective, safe, and relatively simple accessory therapy with a low morbidity rate. An adjunctive trial would seem to be most justified in the T_1 N_1 M_0 lesions, particularly in adenocarcinoma and undifferentiated large cell carcinoma where the implications of positive tests for hilar lymph node involvement are more serious.

In clinical stage II disease, 65% of all patients die of recurrent or metastatic disease at 18 months. Thus, we have strong evidence for adjunctive therapy in this group, and it is felt that a large-scale cooperative clinical trial is justified at this time. In squamous cell carcinoma, postoperative irradiation might be considered if one assumes that most of these patients die from recurrence at the bronchial stump or due to an error in assessing the status of the mediastinal nodes. In stage II adenocarcinoma and in large cell carcinoma, the 18-month survival rate is approximately 16% as compared to 42% for squamous cell carcinoma. These cell types are associated with a higher incidence of occult systemic disease and thus adjunctive chemotherapy must be considered. A major problem in the design of clinical trials for stage II disease is that only an estimated 6% of the lung cancer patients are in this group.

The 18-month cumulative survival rates in stage III disease, which includes all cases of undifferentiated small cell (oat cell) carcinoma, vary between 4% and 16%, with the exception of superior sulcus tumors which have an estimated survival of 25%. Surgery must still be regarded as the definitive therapy when the tumor is localized and resectable and the extent of mediastinal lymph node involvement is limited to the lower ipsilateral and/or subcarinal lymph nodes (T_1 $N_{2.1}$ M_0 and T_2 $N_{2.1}$ M_0 lesions). The highest priority for cooperative trial in these cases of regional reductive surgery might involve irradiation therapy and/or chemotherapy.

In patients with resectable primary tumors without clinical evidence of disseminated disease but with contralateral mediastinal lymph node involvement, resection cannot possibly encompass the total disease, and thus such treatment becomes "adjunctive reductive surgery" ($N_{2.2}$ and $N_{2.3}$ lesions). Once again the highest priority for clinical investigation should involve irradiation therapy and chemotherapy. Patients with extensive primary lesions, or those with resectable primary lesions but with known disseminated disease, also should be considered for "adjunctive reductive surgery." Superior sulcus tumors represent a small subset of bronchogenic carcinomas and are unique in their biologic behavior. The role of definitive irradiation therapy, especially with utilization of fast neutron beams, remains to be assessed, and such treatment should be compared to the results of preoperative irradiation with resection.

Undifferentiated small cell (oat cell) carcinoma must be regarded as a systemic disease at the time of its diagnosis. Its clinical course is not related to the clinical anatomic extent of the disease. Because of its disastrous biologic behavior, I do not feel that surgery is warranted in the management of oat cell carcinoma if there is histologic proof of its presence.

In conclusion, it can be shown that there are a number of discrete anatomically defined sets within the total population of lung cancer. These can be further statified by the histologic pattern of disease. We can capitalize upon our current knowledge concerning the unique biologic behavior of these subsets in the design of clinical therapeutic investigations, and, by so doing, we will tend to approach a more optimal plan for research.

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Keynote Address on Chemotherapy for Lung Cancer

Heine H. Hansen [1]

In general, major progress in the management of malignant disease has resulted from surgical and radiotherapeutic approaches, particularly in patients with localized disease. However, forms of systemic treatment are required for malignant disease which is disseminated at the time of diagnosis. According to data accumulated by Cutler from the State of Connecticut (1), more than 50% of all patients with lung cancer fall into the latter category. Chemotherapy is, at present, the major option for systemic treatment of bronchogenic carcinoma.

Within the last decade, chemotherapy, applied either alone or in combination with radiotherapy or surgical treatment, has substantially improved the survival and the quality of life in patients with malignant lymphoma, malignant trophoblastic tumors, childhood leukemia, neuroblastoma, or Wilms' tumor. Unfortunately, improvement cannot be claimed for the major types of bronchogenic carcinoma, in spite of extensive clinical trials described in more than 400 publications within the last 15 years. Recent studies have indicated, however, a definite role for chemotherapy in the management of bronchogenic carcinoma in general and, more specifically, small cell carcinoma. It might be worthwhile to focus on these achievements after we review some of the basic steps in the present system for developing more successful treatment programs.

At present, clinical research studies include the following steps:

1. Preclinical screening of antineoplastic agents with special reference to clinical application in bronchogenic carcinoma.
2. Development of a uniform system for the screening of the clinical activity of single agents (phase II studies).
3. Development of controlled chemotherapeutic trials (phase III studies) in accordance with stage and cell type using chemotherapy alone or in combination with surgical treatment and/or radiotherapy and/or immunotherapy.

Initial clinical trials (phase I studies) are deliberately excluded from this discussion since they explore host tolerance rather than the antitumor effect of new agents.

In the preclinical animal system, emphasis, for a long period of time, has been devoted to selective animal tumors such as L1210 leukemia, Walker's P32 carcinoma, and others. To some degree, all of these tumors have been useful as screening tumors with regard to the prediction of results in fast-growing human neoplasms, including the efficacy of each individual agent and the development of optimal dose schedules. The findings indicate that the cell kinetic pattern of the L1210 system is similar to that in leukemia in man. A model for bronchogenic carcinoma in man that takes into consideration the different growth rate of each cell type is not available yet (2).

The addition of the Lewis lung tumor to the screening system might be advantageous however. The Lewis lung tumor in BDF_1 mice is characterized by a cell kinetic pattern that is consistent with that in malignant solid tumors in man with respect to the decrease in the fraction of actively proliferating cells observed along with an increase in the size of the tumor (3). The average pulse thymidine index is about 18% for a primary Lewis lung tumor compared with 37% for the small lung metastases (3). In comparison, it is of interest that Muggia and associates, applying intratumoral injections of tritiated thymidine into metastatic lesions in patients with small cell carcinoma of the lung, recently demonstrated a median labeling index of 16.7% with an increase to 52% in 46 hours (4).

[1] Bispebjerg Hospital, Copenhagen, Denmark.

Of further interest in regard to the Lewis lung tumor is the observation that surgical treatment followed by treatment with a combination of methyl-CCNU and cyclophosphamide [2] produced a substantial "cure" rate for advanced solid and metastatic Lewis lung carcinoma, whereas surgical treatment alone and chemotherapy alone were only palliative. In addition, a potentiating effect was noted when a nitrosourea was used in conjunction with cyclophosphamide (5). The potentiation of these two agents is not an isolated phenomenon for the Lewis lung tumor per se, but has also been demonstrated in AK lymphoma (6) and L1210 (7) systems. It is, therefore, noteworthy that a similar effect has been observed in patients with extensive bronchogenic carcinoma.[3] A combination of cyclophosphamide, a nitrosourea (CCNU), and methotrexate [4] showed statistically significant superiority over a combination of cyclophosphamide and methotrexate in patients with small cell carcinoma when both groups were treated to equal toxicity (table 1). It would be interesting, therefore, to try this drug combination in conjunction with surgical treatment and/or radiotherapy in patients with early small cell carcinoma. These results further emphasize the necessity of a closer working relationship between the preclinical screening programs and the clinician.

Regarding the next step, the phase II trial (evaluation of the effectiveness of new antineoplastic agents that have shown activity in the preclinical trials), at least two factors need to be emphasized: (*a*) the necessity of subclassification by cell type; and (*b*) the definition of the parameters used for the evaluation of the therapeutic effectiveness of a compound.

TABLE 1.—Comparison of a two-drug combination with a three-drug combination in the treatment of extensive small cell carcinoma of the lung

Treatment	No. of patients	Duration of treatment until progression (days)
Cyclophosphamide + methotrexate	17	94*
Cyclophosphamide + methotrexate + CCNU	19	180*

*P value < 0.05 (modified Wilcoxon test).

The importance of describing cell type is observed not only in comparisons of antineoplastic agents with different modes of action, but also in comparisons of compounds with apparently similar biochemical effect, such as the alkylating agents. For example, data from the VA Cooperative Lung Group indicated that mechlorethamine [5] had the highest activity in the treatment of patients with extensive epidermoid carcinoma when survival was used as the criterion, whereas the most active compound for extensive small cell carcinoma was cyclophosphamide (8). Both differences were statistically significant at the 0.05 level. Similar differences of activity according to cell type within the group of alkylating agents are recognized when objective response is used as a parameter of effectiveness (9).

From the latter two observations the obvious question arises concerning the correlation between survival and objective response rate. A statistically significant correlation was reported in at least two studies where both parameters were evaluated—a study by the Eastern Cooperative Oncology Group comparing radiotherapy versus radiotherapy and chemotherapy (10), and a study by Hansen et al of intensive combination chemotherapy and radiotherapy (11). It is obvious, however, that tumor measurement at its present stage is a highly unsophisticated method for evaluation of change

[2] Methyl-CCNU: NSC-95441; CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-.

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

[3] Hansen, H. H., Carr, D. T., and Sealy, R. Unpublished data.

[4] Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

[5] Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride; HN2; nitrogen mustard.

in the size of a tumor. The recent introduction of the fiberoptic bronchoscope might facilitate future evaluations.

One additional parameter that might be used as a refinement for a quantitative evaluation of tumor response is the characteristic production of ectopic hormonal markers in bronchogenic carcinoma, particularly small cell carcinoma. The number of detectable ectopic hormones has increased considerably and the quantitative methods for measurement of these hormones have lately been much refined.

With regard to comparative controlled clinical trials (or phase III trials), a number of factors must be considered in addition to the evaluation of the results according to cell type. These include, among others, the questions of a single drug versus combination chemotherapy in order to achieve maximum cell kill, optimal scheduling of treatment with the compounds, duration of chemotherapeutic treatment, intermittent versus maintenance treatment, treatment until progression of disease versus rotation of single agents and/or combinations and the relationship to drug toxicity, and chemotherapeutic effectiveness. The last factor was emphasized by Karrer et al in a retrospective analysis of postoperative treatment with cyclophosphamide in which leukopenic patients were compared with either nonleukopenic or untreated patients (12).

Finally, the question arises regarding the stage of the disease at which chemotherapy should be started.

Chemotherapy has been applied as an adjunct to surgical treatment and radiotherapy in both patients with extensive disease and patients supposed to have local disease. In general, the results of all controlled clinical studies have been negative in patients with extensive disease with regard to significant prolongation of survival. Brunner et al (13) have even demonstrated unfavorable effects of adjuvant chemotherapy, reporting a statistically significant higher cumulative incidence of metastases occurring in a cyclophosphamide-treated group as compared with a control group including all cell types but predominantly squamous cell carcinoma. This phenomenon might indicate interference with host-tumor factors. Other recent data have, on the other hand, demonstrated highly suggestive evidence of superiority in survival in patients with resectable small cell carcinoma treated with cyclophosphamide as compared with a control group (14). Similar differences were not observed in the other cell types. Similarly, more than ten prospective studies of combined chemotherapy and radiotherapy in patients considered to have regional nonresectable bronchogenic carcinoma have had negative results. In contrast, a significant increase in the median survival time from 114 days in a group treated with radiotherapy to 192 days in a group treated with combination therapy (intermittent high doses of cyclophosphamide in combination with radiotherapy) was recently reported by Bergsagel et al (15). In addition, a statistically significant delay in the occurrence of metastatic lesions outside the irradiated field was noted in the group treated with chemotherapy. The observations were particularly pronounced for the group with small cell carcinoma (15).

In summary, it appears from these data that chemotherapy now has a definite role in the treatment of patients with small cell carcinoma of the lung. With the application of more intensive chemotherapy with combinations of drugs with different modes of action and optimal use of each component at the optimal time, this role might be expanded to include other cell types of lung cancer to a significant degree.

It is my hope that the Chemotherapy Panel at this First International Workshop for Therapy of Lung Cancer will update current therapeutic experience and actively participate in the next steps to be taken for future studies.

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Keynote Address on Immunology and Immunotherapy

Lucien Israel [1]

It is as a therapist and not as an immunologist that I was asked to act as coordinator for the Panel on Immunology. Our task was not to discuss the fundamentals of immunology but to select from available knowledge what can be immediately tested in clinical studies and in therapeutic trials.

The first panel session was devoted to the evaluation of the immunologic status of lung cancer patients, as related to cell type and stage of disease, and changes of the immunologic status under the influence of various types of therapy; the second session was devoted to approaches of immunotherapy.

I would like to underline a few points about the contents of each of the panel sessions.

EVALUATION OF IMMUNOLOGIC STATUS AND PROGNOSIS

Evaluation of the cell-mediated immune response in patients with lung cancer has been described previously. Based on these data and on previous discussions by members of the Working Party for Therapy of Lung Cancer, Drs. R. Ritts, H. Takita, and I prepared a skin test protocol for consideration by the Panel.

The following additional points were presented by the panelists:

1. Unresponsiveness of cell-mediated immune response of skin tests is common in cancer patients in general and lung cancer patients in particular.
2. Unresponsiveness is seen even in "early" stages of disease.
3. Patients with negative or "weak" skin tests are more likely to have metastases than patients with strongly positive skin tests.
4. The survival curves of patients undergoing radical resection differ significantly according to the preoperative response to tuberculin skin test.

Hence, it seems well established that the immunologic status of these patients, as evaluated by skin tests, has prognosis significance, and it was proposed that in clinical trials patients be stratified according to response to skin tests.

On the other hand, data from the treatment of malignant diseases other than lung cancer have shown that the correlations between the cell-mediated immune response and the so-called immunodepressing effect of anticancer drugs are not at all linear. E. Hersh and associates have shown that patients with good tumor response may convert from a negative to a positive delayed hypersensitivity response while receiving therapy, whereas unresponsive patients convert from a positive to a negative response. We have similar data to confirm these findings.

It will be proposed, therefore, that patients be followed by repeated skin tests every 2 or 3 months during any kind of therapy, and that the response to skin tests be correlated to prognosis, to tumor response, and to different chemotherapeutic regimens and schedules.

Many papers published in recent years, including a well-documented paper by R. Sealy and his colleagues, have discussed the immunodepression of T cells, and especially the adverse effects on such cells during radiotherapy for breast cancer, and, concomitantly, the adverse effects of this immunodepression on prognosis. I personally think that this effect could be due not only to the irradiation of the sternum and ribs but also to the irradiation of the thymus. It seems at this point necessary to extend these observations to the immunologic status of patients who received radiotherapy for lung cancer.

[1] Centre Hospitalier Universitaire Lariboisiere, Paris, France.

IMMUNOTHERAPY

Immunotherapy of cancer in general is still in its very early stages, and immunotherapy of lung cancer has only been tried in a very small number of institutions. However, our main task is not and will not be to wait for well-established results and to duplicate conclusive studies, but to try to improve the end-results in lung cancer by means of new weapons and new combinations of weapons. Panelists discussed how immunotherapy has been applied by themselves to lung cancer and to other malignant diseases and what could be done now. R. Ritts proposed and discussed a pilot study with transfer factor that is very appealing. H. Wrba shared with us his experience with immunologic considerations for lung cancer, and D. Mortin discussed his experience with Bacillus Calmette-Guérin (BCG) in melanoma and other malignancies. E. Hersh presented the results of his studies on childhood leukemia. My own presentation was devoted to nonspecific immunostimulation with *Corynebacterium parvum* and BCG, including some unpublished results.

A few points for discussion include the following:

1. It is not true, though it has been generally accepted, that immunotherapy is effective only in residual disease. We have unquestionable data on effectiveness of immunotherapy in advanced disease. Moreover, immunotherapy combined with chemotherapy does not result, as assumed by many, in deeper immunosuppression but in better tumor response and immunoprotection in advanced disease. I hope that, after having discovered the best cytostatic treatments, chemotherapists will agree on comparative trials with and without immunotherapy.
2. Patients who have tumor resection in early stages of their disease would probably benefit from some immunotherapy. Some surgeons and radiotherapists, fearing complications, will not employ immunotherapy in these patients. I want only to remind them that their results have not improved for years, and that it is simply our duty to try some additional therapy, at least in well-designed pilot studies.
3. It has been sufficiently shown that not only are the specific defenses depressed in cancer patients, but the nonspecific, general, cell-mediated, immune responsiveness is also depressed, sometimes before the first malignant cell appears.

It seems to me that any kind of cancer immunotherapy must include nonspecific stimulation of the reticuloendothelial system by means of, for example, BCG and/or *C. parvum*, and that we must accept minor inconveniences from this kind of stimulation if we want to progress. This, of course, is a personal opinion, submitted for discussion.

I hope that we will agree, at least, on some pilot studies of nonspecific immunotherapy in different subgroups of patients, including good risk patients. We must find out by ourselves, without conceptual fears and with the true consent of our patients, what really lies behind the term "immunotherapy." All the knowledge accumulated in this area seems to indicate that this field of therapy could be enormously gratifying.

Keynote Address on Biostatistics and Data Retrieval [1]

Marvin Zelen [2]

At this International Workshop we are attempting to review the past and plan for the future with regard to bronchogenic carcinoma. Our past experience looks dismal, and future prospects look uncertain. Yet we all know how to prevent bronchogenic carcinoma. I hope that in addition to the scientific recommendations for future research generated by this Workshop, we will have a strong recommendation urging all countries to become much more aggressive in restricting smoking. This is one disease we can eradicate with appropriate public health measures.

Plans for the Panels

The two panels on Biostatistics and Data Retrieval will be mainly concerned with prospective clinical trials. The first panel will discuss (*a*) recent experiences with some clinical trials on lung cancer, and (*b*) the role of the natural history of lung cancer in relation to the planning of clinical trials. The emphasis will be on the methodologic problems which arise in extracting meaningful results from such studies.

The second panel will take up the general problems of planning prospective clinical trials. Among the topics we expect to discuss are:

(*a*) What are the factors influencing prognosis and response to therapy? Are the prognostic factors which are important for surgical patients also important for nonoperable patients?

(*b*) What are the general scientific principles to be used in planning clinical trials? How important is randomization? How many patients are necessary in a trial? How does one balance out among the therapies the known prognostic factors which affect the outcome?

(*c*) To what populations of patients do our inferences from clinical trials apply? Are our clinical trials using "selected" patients? Are the patient populations in the institutions which participate in clinical trials typical?

(*d*) What does one do about the quality control of the data? What are the responsibilities and obligations of investigators?

(*e*) Are there new designs for planning phase I and II trials? How good are our current experimental plans? One of the keynote speakers has noted that many new chemotherapeutic agents may have received an inadequate trial due to poor experimental design.

(*f*) How important is histology when evaluating the results of treatment relative to other variables? Several of the keynote speakers discussed the role of histology. Is it the most important factor when evaluating benefit from therapy? Are there other important variables which are being neglected?

(*g*) What are appropriate end-points to judge therapy? Should we take into account the quality of survival? Is it possible to standardize the evaluation of nonmeasurable tumors? Are such evaluations at all useful?

(*h*) Finally, are there new statistical techniques for analyzing data?

Personally, I'm tired of sitting in conferences, very similar to this one, where investigators religiously intone that two treatment groups were statistically significant at some miniscule probability level. These kinds of statements do not really communicate what is going on.

I am sure these topics will be discussed not only in our two sessions, but in the other sessions as well. After all, these questions and ideas are interdisciplinary and are important in the conduct of all future medical experiments.

[1] Supported by grants CA-10810 from the National Cancer Institute, National Institutes of Health, and V101 (134)P-64 from the Veterans' Administration.

[2] State University of New York at Buffalo.

Performance Status and Histology as Prognostic Variables for Extensive Disease

The Veterans' Administration Lung Study Group (VALSG) has been conducting randomized prospective clinical trials since 1957 on patients with advanced (inoperable) lung cancer. The two major disease subgroups in these trials are termed *limited* and *extensive* disease patients. *Limited disease* patients are characterized by (*a*) disease confined to one hemithorax, although local extensions may be present; (*b*) no extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same portal as the primary tumor; and (*c*) primary tumor and regional nodes which can be adequately treated and totally encompassed in every portal. *Extensive disease* patients are inoperable patients who cannot be classified as having limited disease. During the course of several trials, one of the treatment groups received a placebo. That is, patients were randomly assigned to a placebo treatment. This group of patients represents a valuable resource for studying the natural history of the disease. Figures 1 and 2 depict the survival distribution for these two disease subgroups.

Table 1 summarizes the median survival by cell type and figures 3 and 4 summarize the survival distributions. The term "other cell" refers to cell types other than the four principal classifications.

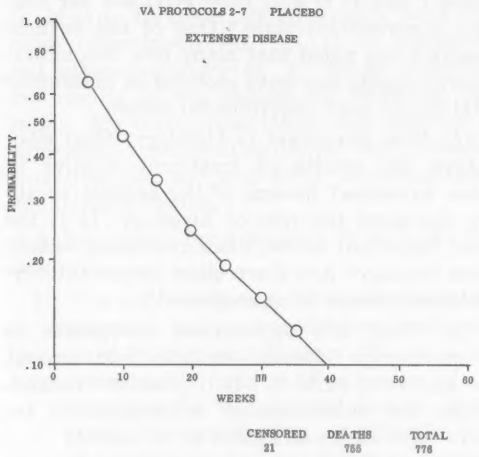


FIGURE 1.—Survival distribution of extensive disease (placebo) patients.

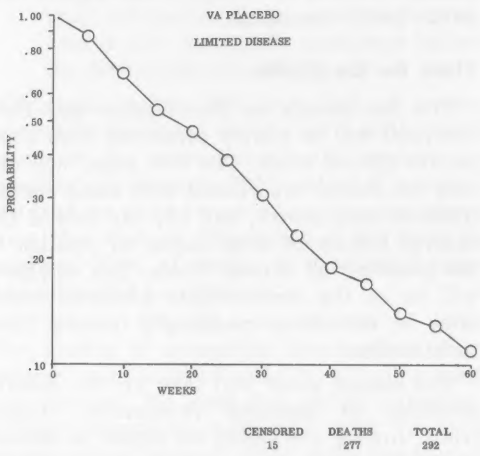


FIGURE 2.—Survival distribution of limited disease (placebo) patients.

TABLE 1.—Effect of cell type on median survival for extensive and limited disease patients

Cell type	Extensive disease		Limited disease	
	Median survival (wks)	No. of patients	Median survival (wks)	No. of patients
Squamous cell	9.4	294	15.7	130
Small cell	5.0	108	11.7	38
Large cell	11.1	124	22.4	26
Adenocarcinoma	6.9	104	15.1	37

Another variable on which information was gathered was the "performance status" of each patient at the time of entry into the study. This was done using the Karnofsky scale. Table 2 summarizes this scale. The scale ranges from a low of 1 (indicating a moribund patient) to a high of 10 (patients with no evidence of disease and carrying out normal activities). Figures 5 and 6 are semi-log plots of the median survivals of the extensive and limited disease patients (placebo group) versus their initial performance status. The plots are most remarkable! There is a clear linear relationship between the logarithm of this median survival time and the initial performance status. The lower the initial performance status, the less time the patient will live. It is evident that the variation of survival is much greater with regard to performance status than to the four histologic types. Figures 7 and 8 give the survival plots.

Figures 9 and 10 depict the median survival versus performance status by cell type for extensive and limited disease respectively. The effect of the cell type is to change the intercept of the relation between log median survival and performance status. The slope is approximately the same. It is obvious that when evaluating survival for extensive disease patients, the performance status may be more important than the histology.

Figures 11–18 show the survival distribution by cell type when the patients are classified according to performance status for both the extensive disease and limited disease patients. Again we observe that the variation within a particular cell type is far more important as a prognostic variable than the survival differences between cell types ignoring performance status.

Failure to take performance status into account when evaluating different therapies results in data which have substantial variation. This will result in a large chance of missing important differences between therapies. Without accounting for performance status, the clinical trials will be insensitive for finding real differences between therapies unless there are very large numbers of patients or very large treatment differences.

There are other prognostic variables which also may be of some importance in evaluating therapies. Table 3 summarizes the median survivals (extensive disease, placebo patients)

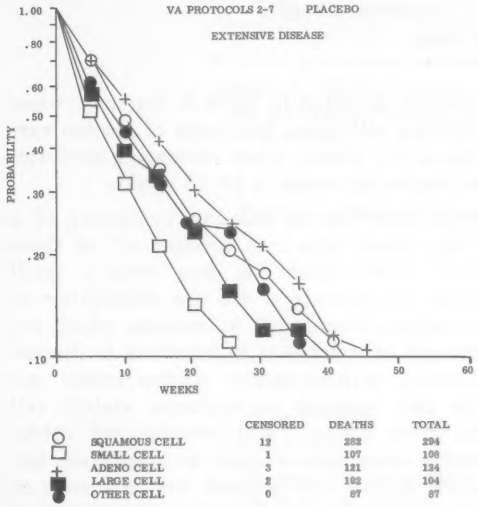


FIGURE 3.—Survival distribution of extensive disease (placebo) patients by cell type.

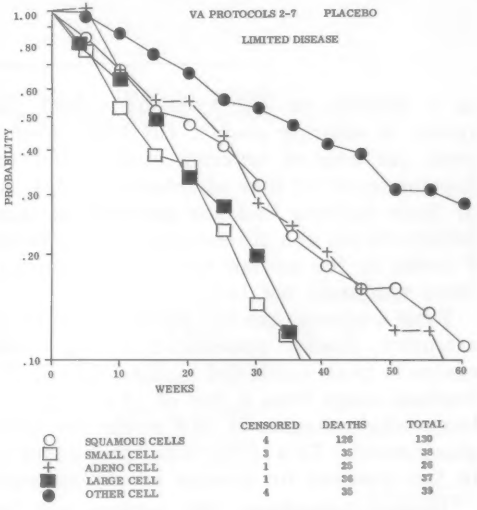


FIGURE 4.—Survival distribution of limited disease (placebo) patients by cell type.

TABLE 2.—Performance status scale (Karnofsky)

Able to carry on normal activity; no special care is needed	10	Normal; no complaints, no evidence of disease
	9	Able to carry on normal activity; minor signs or symptoms of disease
	8	Normal activity with effort; some signs or symptoms of disease
Unable to work, able to live at home, cares for most personal needs; a varying amount of assistance is needed	7	Cares for self, unable to carry on normal activity or do active work
	6	Requires occasional assistance, but is able to care for most of his needs
	5	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	4	Disabled; requires special care and assistance
	3	Severely disabled; hospitalization is indicated, although death not imminent
	2	Very sick; hospitalization necessary; active supportive treatment necessary
	1	Moribund; fatal process progressing rapidly
	0	Dead

as a function of (*a*) 10-pound weight loss (prior to entering study), (*b*) CNS involvement (at time of entering study), and (*c*) hepatomegaly (at time of entering study). All of these indicate that the presence of these factors results in a difference of approximately 6 weeks in the median survival compared to these symptoms not being present.

Table 4 summarizes the median survival for extensive disease patients receiving single agents in trials conducted by the VALSG. The medians range from a low of 13.6 weeks for hexamethylmelamine to 18.9 weeks for cyclophosphamide.[3] This is the same range observed in the presence or absence of extrathoracic symptoms as noted in table 3. Further, when comparing cell types, the range of median survivals is 6–7 weeks; when comparing performance status the range is 20–25 weeks.

It is clear that an adequate evaluation of a therapy must take into account all of these factors. This cannot be done with a small number of patients if we are attempting to demonstrate therapeutic advantages which are measured in months. It is ludicrous to discuss evaluation of lung cancer studies unless one takes into account performance status, cell type, prior therapy, and thoracic and extrathoracic symptoms. Failure to take these important factors into account will introduce so much variability and bias into the trial that real differences between therapies are likely to be missed altogether.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

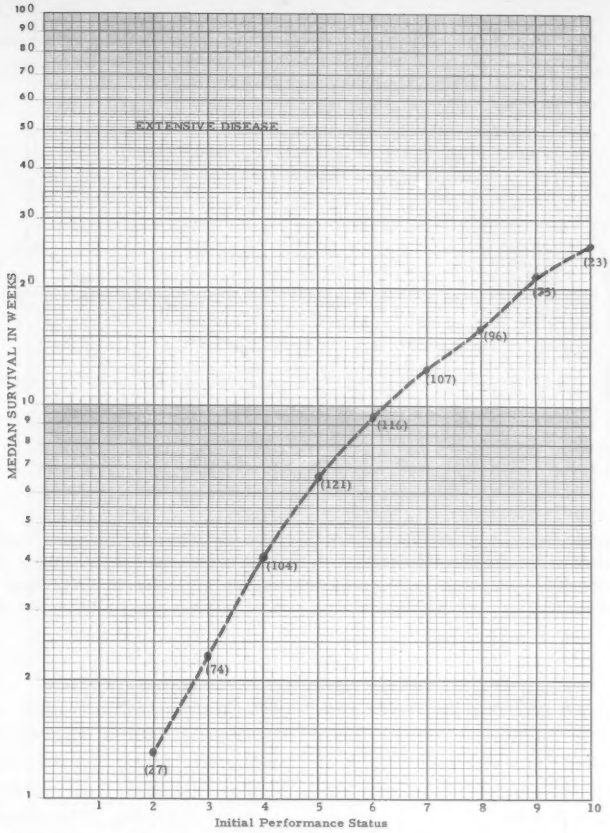


FIGURE 5.—Median survival of extensive disease (placebo) patients by performance status. Numbers in parentheses refer to numbers of patients.

TABLE 3.—Some prognostic factors influencing median survival: Extensive disease*

Factor	Median survival† (wks)	
	Factor present	Factor absent
10-lb weight loss	13.1 (n = 287)	18.7 (n = 713)
CNS involvement	12.2 (n = 151)	18.2 (n = 857)
Hepatomegaly	12.8 (n = 237)	18.4 (n = 759)

*Source: VA Lung Study Group.
†n = No. of patients

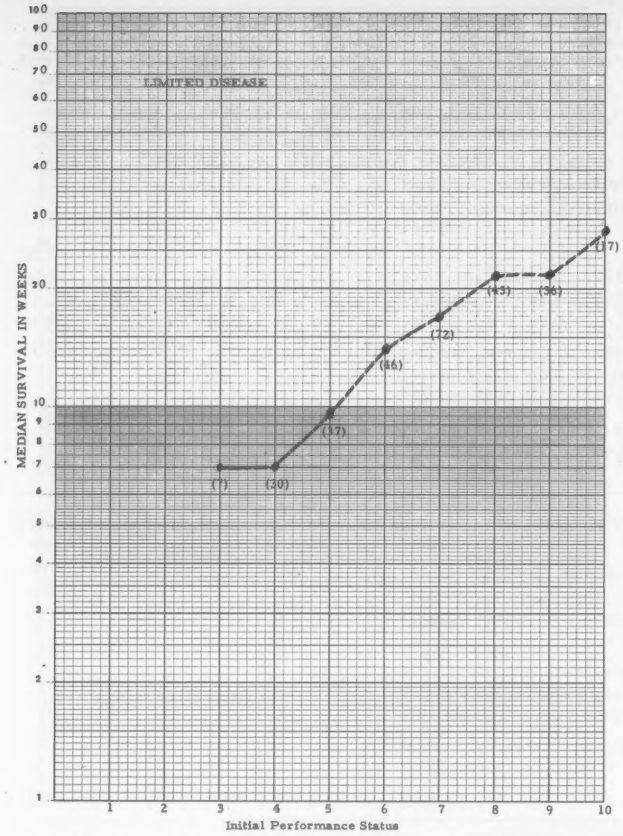


FIGURE 6.—Median survival of limited disease (placebo) patients by performance status. Numbers in parentheses refer to numbers of patients.

TABLE 4.—Median survival of extensive disease patients receiving single drug therapy (unadjusted)*

Drug	Median survival (wks)	No. of patients
Cyclophosphamide	18.9	311
Hexamethylmelamine	13.6	85
Streptozotocin	15.3	114
CCNU	15.9	81
NSC-45388	18.3	101
Dibromodulcitol	18.4	123

*Source: VA Lung Study Group.

Randomization, Replication, and Balance

The three basic ideas in planning clinical trials are *Randomization, Replication,* and *Balance.*

Randomization acts as insurance which protects the trial and the investigator against conscious or unconscious biases.

Replication is needed to assure sufficient numbers of patients so that treatment differences can be detected.

Balance among treatment groups assures that the groups are more alike in all the important prognostic variables and somewhat re-

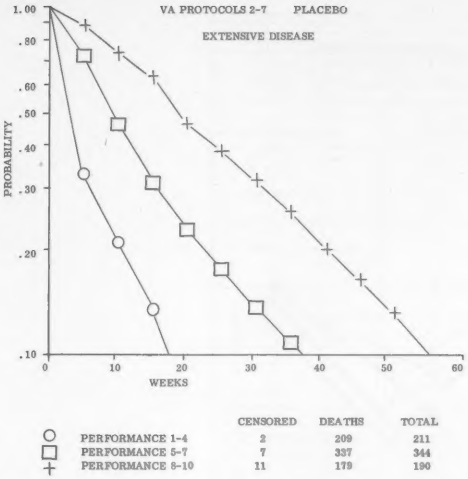


FIGURE 7.—Survival distribution of extensive disease (placebo) patients by performance status. The performance status has been divided into three groups (1–4, 5–7, 8–10) due to the small numbers of patients.

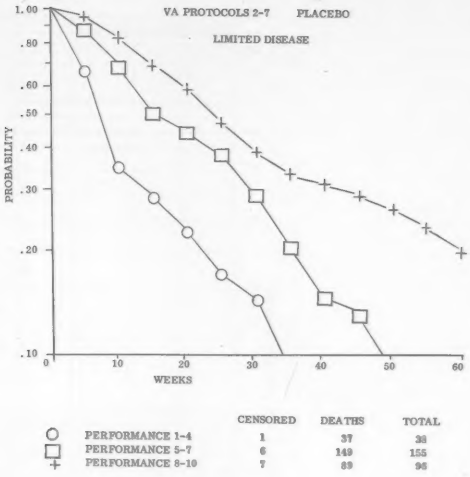


FIGURE 8.—Survival distribution of limited disease (placebo) patients by performance status. The performance status has been divided into three groups (1–4, 5–7, 8–10) due to the small numbers of patients.

moves the reliance that randomization will guarantee treatment groups which are exactly alike. This is accomplished using *stratified randomization* in making up the initial schedule for assigning treatment to patients.

Most clinical investigators will agree that randomization is essential when one is conducting a trial comparing two or more therapies. One of the most important principles in conducting these trials is that the treatment groups which are to be compared are alike in every way except for the treatment modality. Randomization assures, on the average, that this will happen. Many trials have been conducted in the past where a treatment group is compared with a retrospective series. Unless the therapeutic benefit is startling, the comparison with retrospective groups is not to be trusted. Randomization is the key element of the trial which makes the treatment groups comparable. However, keep in mind that the randomization guarantees that the treatment groups are equally heterogenous on the average. It is quite possible that hidden in one of the treatment groups is a relatively homogenous subset of patients who are responding very well to the therapy, but this effect may be hidden when one compares the overall average results of one treatment group to those of another. The trial should have a sufficient number of patients so that homogenous subgroups of patients can be formed on a post hoc basis for comparing differential treatment response. These subgroups reflect cases having approximately the same disease status at the time of entering the trial.

Phase II Trials

Often phase II trials are conducted with only one dose and at only one schedule. There is no reason to believe that this schedule and dose is anywhere near optimum with regard to therapeutic effect. From animal studies we fully know that the therapeutic effect of many active agents depends very much on the dose and schedule. It is time we introduced different schedules and different doses in all phase II trials.

Phase II trials are usually attempted in patients who have failed to respond to known

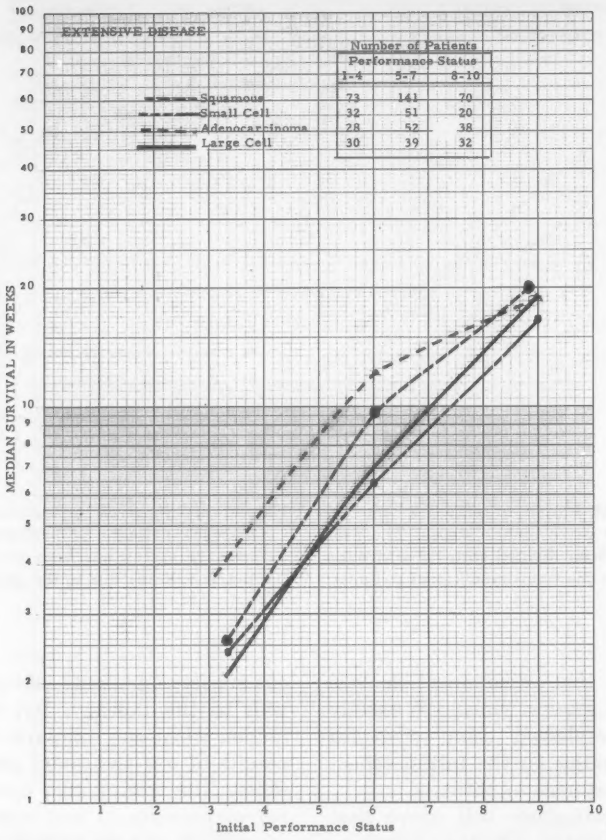


FIGURE 9.—Median survival of extensive disease (placebo) patients by performance status for each major cell type.

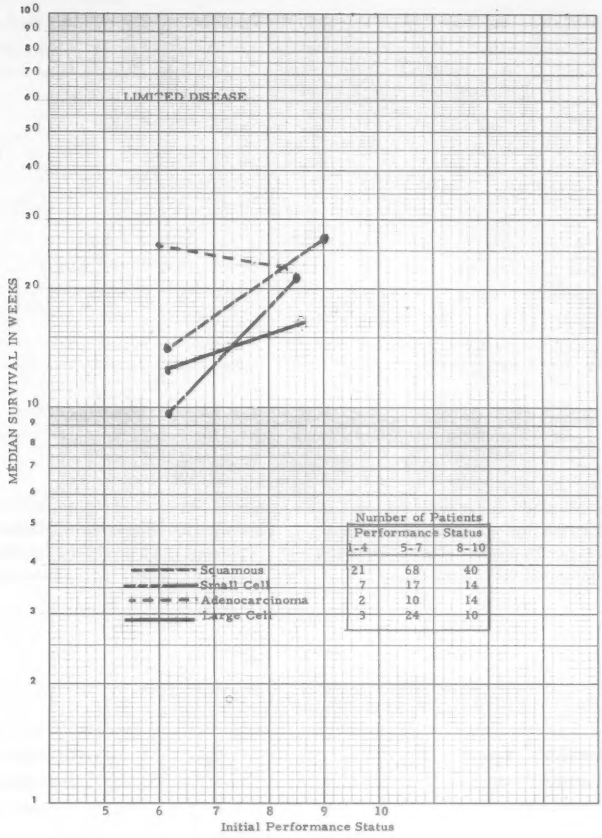
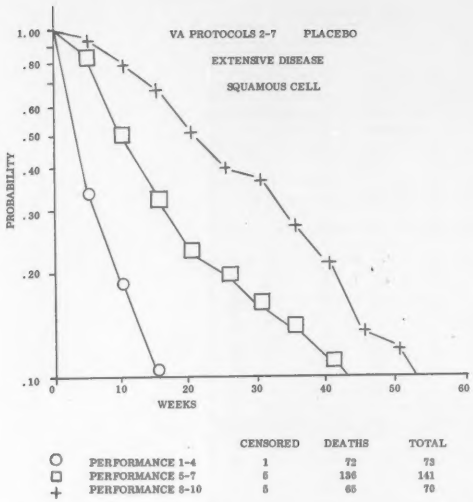
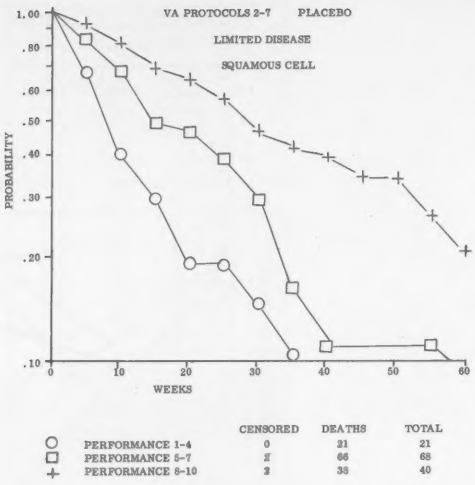


FIGURE 10.—Median survival of limited disease (placebo) patients by performance status for each major cell type.



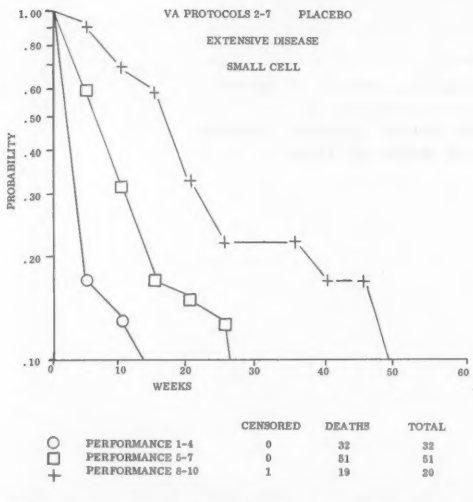
	CENSORED	DEATHS	TOTAL
○ PERFORMANCE 1-4	1	72	73
□ PERFORMANCE 5-7	5	136	141
+ PERFORMANCE 8-10	5	65	70

FIGURE 11.—Survival distribution of extensive disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for squamous cell carcinoma.



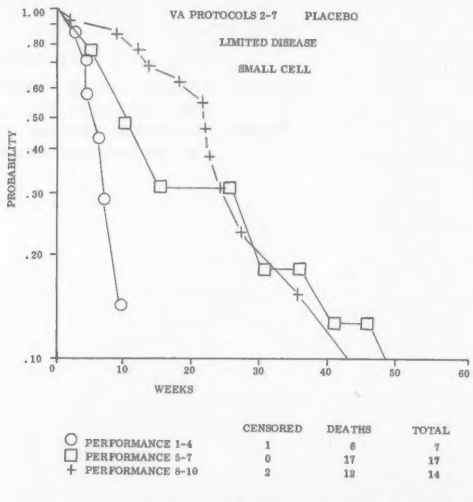
	CENSORED	DEATHS	TOTAL
○ PERFORMANCE 1-4	0	21	21
□ PERFORMANCE 5-7	2	66	68
+ PERFORMANCE 8-10	2	38	40

FIGURE 12.—Survival distribution of limited disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for squamous cell carcinoma.



	CENSORED	DEATHS	TOTAL
○ PERFORMANCE 1-4	0	32	32
□ PERFORMANCE 5-7	0	51	51
+ PERFORMANCE 8-10	1	19	20

FIGURE 13.—Survival distribution of extensive disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for small cell carcinoma.



	CENSORED	DEATHS	TOTAL
○ PERFORMANCE 1-4	1	6	7
□ PERFORMANCE 5-7	0	17	17
+ PERFORMANCE 8-10	2	12	14

FIGURE 14.—Survival distribution of limited disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for small cell carcinoma.

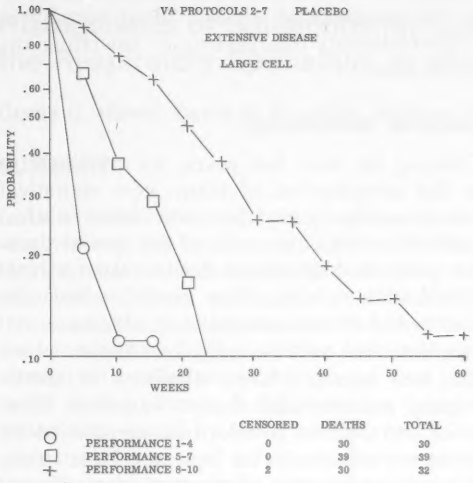


FIGURE 15.—Survival distribution of extensive disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for large cell carcinoma.

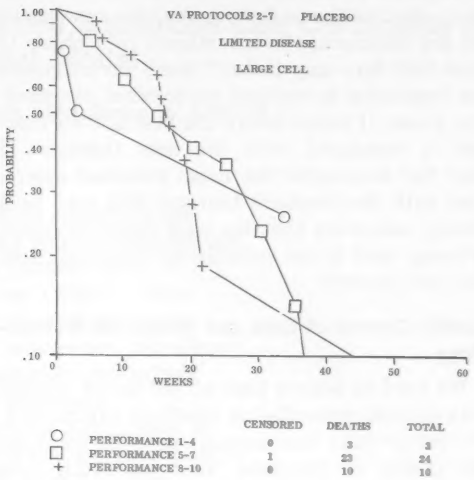


FIGURE 16.—Survival distribution of limited disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for large cell carcinoma.

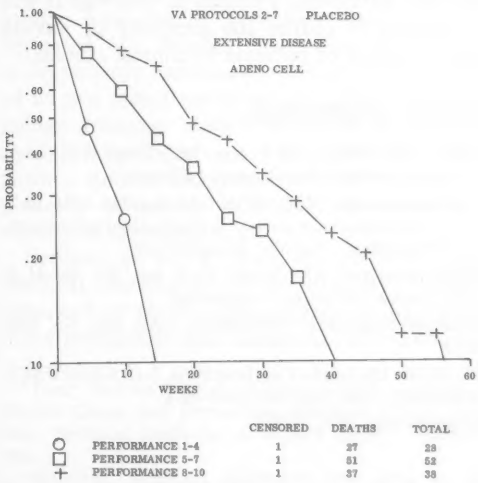


FIGURE 17.—Survival distribution of extensive disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for adenocarcinoma.

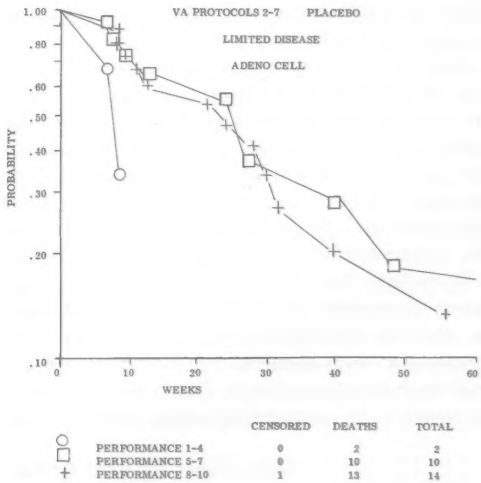


FIGURE 18.—Survival distribution of limited disease (placebo) patients by performance status (groups 1–4, 5–7, 8–10) for adenocarcinoma.

active therapies. If these patients have failed to respond to therapies which are believed active, what makes us believe that the new agent we are attempting to investigate in a phase II trial will fare any better? Some investigators are beginning to conduct randomized comparative phase II trials where the best known therapy is compared with the new therapy. If they fail to observe the usual response associated with the standard therapy, this may be a strong indication that the case material which is being used is not suitable to adequately test the new therapy.

Quality Control of Data and Statistical Methodology

We tend to believe that all published clinical data or data presented at meetings are correct. We rarely take into account or even think of the quality of the data. That is, is the data what it purports to be? Good quality data do not come easy in multi-clinic trials. The quality of the data is only as strong as its weakest link. This not only includes data-handling personnel, but the institutions and investigators who are collecting the data. A problem in multi-clinic randomized studies is investigators who try to circumvent the randomization assignment. They wreck our studies. They have no group discipline and do not belong in multi-clinic trials.

One of the most important factors influencing the quality of a study is the forms which are used to record the data. Not only must the forms ask for the correct scientific information, but they must be designed in such a way that the data can be retrieved and used in analyses. Care must go into designing forms for studies. We must avoid asking for so much secondary information that either the investigator "collapses in horror" at filling out a clinical studies form or the statistical office "drowns" in processing non-essential information. Care must be taken to make the forms as self-coding as possible. By self-coding I mean that the answers to questions on a form can be keypunched or directly put on magnetic tape without the necessity of an individual (usually a nonprofessional) interpreting or rewriting the information.

Statistical Methodology

During the next few years, we are likely to see the introduction of many new statistical techniques for analyzing data from clinical trials. This will be a result of the special problems generated by clinical trials. New methods of statistical analyses are needed which are directly suited to these special problems.

Statisticians will be using techniques which take into account large numbers of demographic, patient, and disease variables. That is, we will be able to take into account 20–50 ancillary variables in an analysis. Data banks of past information for particular disease sites will be established. These data banks will enable us to utilize past information in analyzing current studies. The information on experimental therapies generated by prospective clinical trials will be adjusted for the large number of ancillary variables which may affect the therapeutic outcome. The adjustments for ancillary variables will be made from the data in a data bank. Perhaps in this way it will be possible to reduce the necessity of having large numbers of patients in clinical studies.

LIST OF COMPOUNDS

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Dibromomannitol: NSC-94100; CAS reg. No. 488-41-5; 1,6-dibromo-1,6-dideoxy-D-mannitol

Hexamethylmelamine: NSC-13875; CAS reg. No. 645-05-6

NSC-45388: imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-; CAS reg. No. 4342-03-4

Streptozotocin: NSC-85998

Histogenesis of Squamous Metaplasia and Squamous Cell Carcinoma of the Respiratory Epithelium in an Animal Model

Curtis C. Harris, David G. Kaufman, Michael B. Sporn, and Umberto Saffiotti [1,2]

SUMMARY

An experimental model which compares closely with squamous cell carcinoma of the lung in man is being studied. Syrian golden hamsters are treated with multiple instillations of either benzo[*a*]pyrene (BP), adsorbed on ferric oxide, or *N*-methyl-*N*-nitrosourea (NMU). After treatment, the animals are serially killed and their respiratory tracts are examined by high-resolution light and electron microscopy. Significant ultrastructural lesions which are not seen in the squamous metaplasia found during vitamin A deficiency are found in the squamous metaplasia caused by these carcinogens. Ultrastructural alterations in nuclear structure and defects in the basement membrane are restricted to the squamous metaplasia caused by either BP-Fe_2O_3 or NMU. The ultrastructure of experimentally induced tumor cells is similar to that found in human tumors. Studies on the effect of high doses of vitamin A on the histogenesis of squamous cell carcinoma in the Syrian golden hamster are in progress.

[Cancer Chemother Rep Part 3, vol 4:43–54, 1973]

A number of experimental animal models for human lung cancer have been developed and reviewed (1). Studies concerning experimental respiratory carcinogenesis have been reported at two recent conferences (2,3). The Syrian golden hamster model developed by Saffiotti et al (4) has been one of the most thoroughly studied models. Hamsters have few chronic respiratory infections and are responsive to a variety of carcinogens (1).

Saffiotti et al (4) have shown that intratracheal instillation of benzo[*a*]pyrene (BP) adsorbed on ferric oxide particles causes squamous metaplasia and squamous cell carcinomas (arising most frequently in the hamster tracheobronchial epithelium). The incidence of squamous metaplasia and squamous cell carcinoma was strikingly decreased by the administration of vitamin A starting 1 week after the last exposure to BP-Fe_2O_3 (5).

We are presently investigating the histogenesis of squamous cell carcinoma of the respiratory epithelium as well as determining the effect of vitamin A on this process. We are asking the following questions: First, is the histogenesis of squamous cell carcinoma a *multistage* morphologic process? Second, if this is so, are these stages modified by vitamin A; ie, which stages are reversed, which stages are stabilized, and, finally, which stages are not affected by vitamin A?

EXPERIMENTAL METHODS

The experimental conditions utilized for these studies have been for the most part described previously (6,7). Briefly, the methods

[1] Lung Cancer Branch, Carcinogenesis, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health (NIH), Bethesda, Md.

[2] Excellent technical assistance was given by Mr. Frank Jackson and Mr. Joseph Smith. Photographic aid was expertly provided by Mr. Walter Seewald (Medical Arts and Photography Branch, Division of Research Services, NIH).

used were as follows. Male Syrian golden hamsters (A. R. Schmidt, Madison, Wis) were used in all studies. All groups were maintained on Wayne Lab Blox (Allied Mills, Chicago, Ill) throughout the experiment (table 1). The animals were given intratracheal instillations of either BP-Fe_2O_3 dissolved in 0.9% sterile saline or *N*-methyl-*N*-nitrosourea (NMU)[3] dissolved in 0.15 M sodium citrate buffer, pH 6.5, as outlined in table 1. Groups 2 and 4 are presently being maintained on either a normal diet or excess vitamin A diets, ie, Wayne Lab Blox supplemented by biweekly intragastric administration of either 0.5 or 2 mg of retinyl acetate dissolved in cottonseed oil. The animals are serially killed at 6-week intervals. The respiratory tract is examined by high-resolution light and electron microscopy by methods previously described (6,7). In a parallel study (6), squamous metaplasia in the respiratory epithelium of vitamin-A-deficient hamsters has also been investigated.

SQUAMOUS METAPLASIA OF RESPIRATORY EPITHELIUM

Since the long-term studies outlined in table 1 are still in progress, this report will summarize the data currently available. Attention will be focused upon the histogenesis of squamous metaplasia caused by either carcinogens or vitamin A deficiency.

This interest in studying squamous differentiation and squamous metaplasia is based on the following points: (*a*) Squamous metaplasia *may* be a stage in the histogenesis of squamous cell carcinoma of the respiratory epithelium in man and in animal models. (*b*) The most frequent neoplastic response of the respiratory epithelium of hamster and man is a squamous differentiated tumor, ie, squamous cell carcinoma.

Hyperplasia and/or squamous metaplasia of columnar respiratory epithelium are common responses to infection (8), tobacco smoke (9–11), vitamin A deficiency (6,12), and chemical carcinogens (4,6,13). Thus, comparison of the squamous metaplasia caused by carcinogens with that induced by a *benign* agent or state is important. Since vitamin A deficiency gives rise to a totally reversible squamous metaplasia of the trachea and bronchi, vitamin A deficiency was chosen for study in parallel with carcinogens.

The normal tracheobronchial epithelium of the hamster has been described in detail (7). The luminal ciliated and mucous cells are gen-

[3] *N*-Methyl-*N*-nitrosourea: NSC-23909; CAS reg. No. 684-93-5.

TABLE 1.—Treatment and sacrifice schedule

Treatment group	Carcinogen exposure	Modifying state
	Benzo[*a*]pyrene + Fe_2O_3	
1	5 mg each, Monday, Wednesday, Friday; 10 intratracheal instillations	Normal vitamin A
2	3 mg each, weekly; 10 intratracheal instillations	Normal vitamin A Excess vitamin A
	N-Methyl-*N*-Nitrosourea	
3	0.5 mg, weekly; 10 intratracheal instillations	Normal vitamin A
4	0.5 mg, weekly; 6 intratracheal instillations	Normal vitamin A Excess vitamin A
		→
		Serial sacrifice (at 6-wk intervals)

erated by basal cells, which sit on a continuous basement membrane. Basal cells can also generate a squamous metaplastic epithelium. Recent evidence suggests that mucous cells are also capable of cell division (Harris et al, unpublished results). Squamous metaplasia is defined as the replacement of the mucous and ciliated cells by squamous cells. By electron microscopy, one can observe evidence of squamous differentiation very early in the daughter cells of the basal cells (6). These early squamous cells have no ultrastructural evidence of either mucous or ciliated differentiation. They do have a marked increase in cytoplasmic fibrils and their desmosomes are better developed than those between the normal tracheobronchial epithelial cells. By high-resolution light and electron microscopy, one can observe a continuum from an early non-cornifying squamous metaplasia to a cornifying squamous metaplasia with keratohyaline granules.

ULTRASTRUCTURAL CHANGES CAUSED BY EITHER CARCINOGENS OR VITAMIN A DEFICIENCY

The results of our previous studies (6,7) are summarized in table 2. Intratracheal instillations of either BP-Fe_2O_3 (6,7) or NMU (Harris et al, unpublished results) cause a variety of acute changes. The luminal cells

TABLE 2.—Histogenesis of squamous metaplasia

Exposure to carcinogen	*Vitamin A deficiency*
A. Increase in lysosomes, dilation of endoplasmic reticulum, and abnormal nucleoli in ciliated and mucous cells	*A.* Flattening of ciliated and mucous cells
B. Abnormal basal cells 1. Pleomorphic nucleoli 2. Nuclear bodies	*B.* Normal basal cells
C. Basal cell hyperplasia	*C.* Basal cell hyperplasia
D. Sloughing of altered ciliated and mucous cells	*D.* Sloughing of altered ciliated and mucous cells
E. Basal cells differentiate into abnormal squamous metaplastic cells 1. *Regular squamous metaplasia* *a.* Cornification *b.* Keratohyaline granules *c.* Abnormal nucleoli *d.* Defects in basement membrane 2. *Atypical squamous metaplasia* *a.* Enlarged nuclei indented by cytoplasmic invaginations *b.* Nucleolar plaques and microsegregation *c.* Defects in basement membrane *d.* Widened intercellular spaces and abnormal cellular junctions	*E.* Basal cells differentiate into normal squamous metaplastic cells 1. Cornification 2. Keratohyaline granules

are sloughed in focal areas, but many of the basal cells persist, divide, and differentiate into abnormal squamous metaplastic cells.

In general, two histologic types of squamous metaplasia are found (table 2; Appendix, figs 1 and 2). *Regular squamous metaplasia* caused by carcinogens cannot be distinguished by conventional light microscopy from that found in benign states. By electron microscopy, significant differences are found in the majority of the carcinogen-induced lesions, eg, pleomorphic nucleoli (Appendix, fig 3) and defects in the basement membrane (Appendix, figs 4*A* and 4*B*). *Atypical squamous metaplasia* was found only in animals exposed to carcinogens. Examination of 1μ sections of Epon-embedded tissue revealed focal replacement of differentiated ciliated and mucous cells by pleomorphic cells (Appendix, fig 2). These pleomorphic cells were polygonal as well as squamous in appearance. Electron microscopic examination revealed that enlarged nuclei were indented by cytoplasmic processes (Appendix, fig 5). They contained abnormal nucleoli (Appendix, fig 6) that were enlarged and frequently multiple in number. Varying degrees of segregation (14) of nucleolar granules and fibrils were found. Widened intercellular spaces and defects in the basement membrane were also found. These ultrastructural lesions were not seen in squamous metaplasia found during vitamin A deficiency (6).

The frequency with which *regular* and *atypical* squamous metaplasias caused by carcinogens progress into invasive carcinomas is not yet known. Microinvasion of squamous metaplastic cells across the basement membrane has been observed in both types of carcinogen-induced metaplasia. It is also unknown how often carcinogen-induced *regular* squamous metaplasia can become an atypical squamous metaplasia and vice versa.

Although it is too early to predict the effect of vitamin A status on the tumor incidence in our current experiments, the vitamin A status of the animal can modify the extent of squamous metaplasia caused by NMU (text, fig 1) (Harris et al, unpublished results). To measure the extent of squamous metaplasia, photomicrographs were taken from cross sections of tracheal rings (seven per animal). The total epithelial length was measured at the basement membrane from the photographic prints. The length of squamous metaplasia was also measured and the results were expressed as percent of total length ± standard error. The extent of squamous metaplasia gradually decreases to a plateau in the animals receiving normal levels of vitamin A. Animals on the excess vitamin A diets have less squamous metaplasia. There is a suggestion that this effect on squamous metaplasia is dose related.

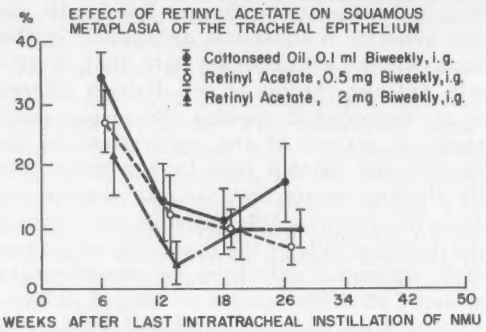


FIGURE 1.—Effect of retinyl acetate on the extent of squamous metaplasia of the tracheal epithelium (Ig = intragastric).

COMMENTS

Using high-resolution light and electron microscopy, we found significant morphologic differences between squamous metaplasia caused by a benign state, vitamin A deficiency, and that caused by either BP-Fe_2O_3 or NMU. Defects in the basement membrane and pleomorphic nucleoli were restricted to carcinogen-induced lesions. Defects in the basement membrane have been described in the bronchi of smoking dogs (11). Similar defects have been described in premalignant and malignant lesions of the mammary gland (15,16), skin (17), hamster cheek pouch (18), and larynx (19).

Changes in nuclear and nucleolar structure are two of the most reliable criteria for the morphologic diagnosis of neoplasia. Enlarged nuclei with irregular contours and pleomorphic

nucleoli are early and persistent findings following exposure to carcinogens.

Although the ultrastructural response of the tracheobronchial epithelium of the hamster to NMU is similar to the response to BP-Fe_2O_3 these carcinogens have different structures and properties. BP is a polynuclear hydrocarbon which requires enzymatic activation to become carcinogenic (20), whereas NMU does not require enzymatic activation. BP is slowly removed from the respiratory tract over a period of several days (21). NMU is degraded at neutral pH in a few minutes (22).

The histologic types of tumors caused by NMU and BP-Fe_2O_3 have been described in detail (4,21,23). With the exception of oat cell carcinoma, the common types of human lung cancer have been induced. The ultrastructure of these experimentally induced tumor cells is essentially the same as that reported for human tumors (24–27) of the same histologic type (Appendix, figs 7–9) (Harris et al, unpublished results). A preliminary report by Blair et al (28) at the 1972 annual meeting of the American Association for Cancer Research suggests that an experimental model for the investigation of oat cell carcinoma may soon be available for study.

APPENDIX

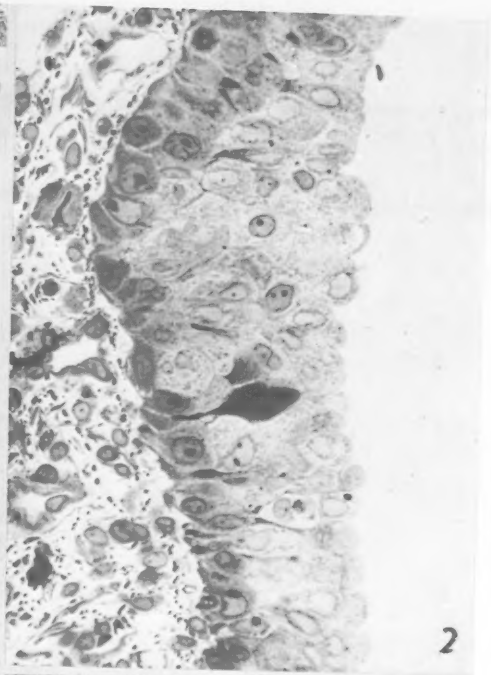
FIGURE 1.—*Regular* squamous metaplasia caused by BP-Fe_2O_3. Four months after last intratracheal instillation (Group 1) (× 100).

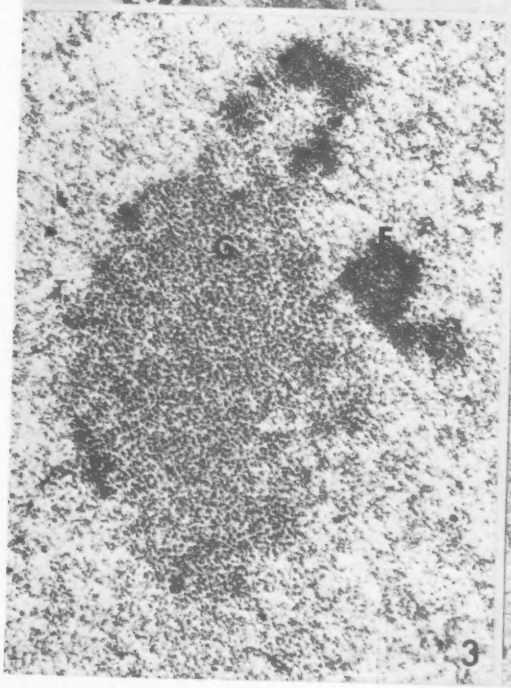
FIGURE 2.—*Atypical* squamous metaplasia caused by BP-Fe_2O_3. Pleomorphic cells varying in optical density. Prominent nucleoli within enlarged nuclei. Two weeks after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 400).

FIGURE 3.—Nucleolar granules (G) are segregated from fibrils (F). Six months after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 18,000).

FIGURE 4*A*.—Cytoplasmic processes crossing the basement membrane. Nine months after last intratracheal instillation of NMU (Group 3) (× 16,200).

FIGURE 4*B*.—Only fragments of basement membrane remaining at epithelial-connective tissue junction. Two weeks after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 26,400).





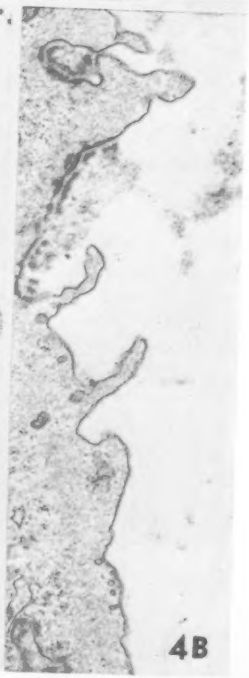
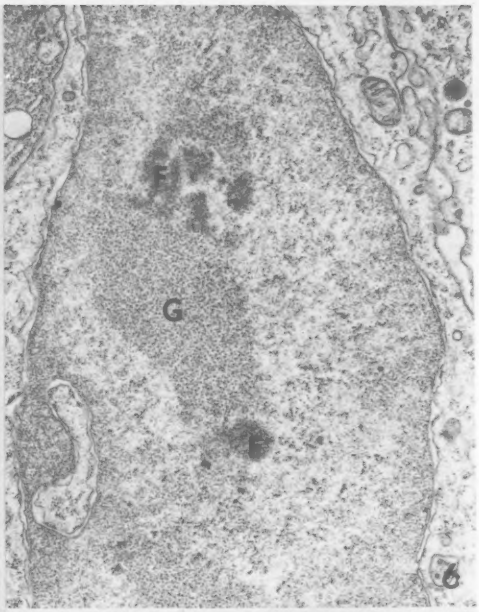


FIGURE 5.—Nucleus is indented by cytoplasmic invagination. Two months after last intratracheal instillation of NMU (Group 3) (× 18,000).

FIGURE 6.—Nucleolar fibrils (F) are segregated from granules (G). Twenty-two months after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 29,600).

FIGURE 7.—Adenocarcinoma. Cell contains large mucous granules (M). Twenty-two months after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 8800).

5



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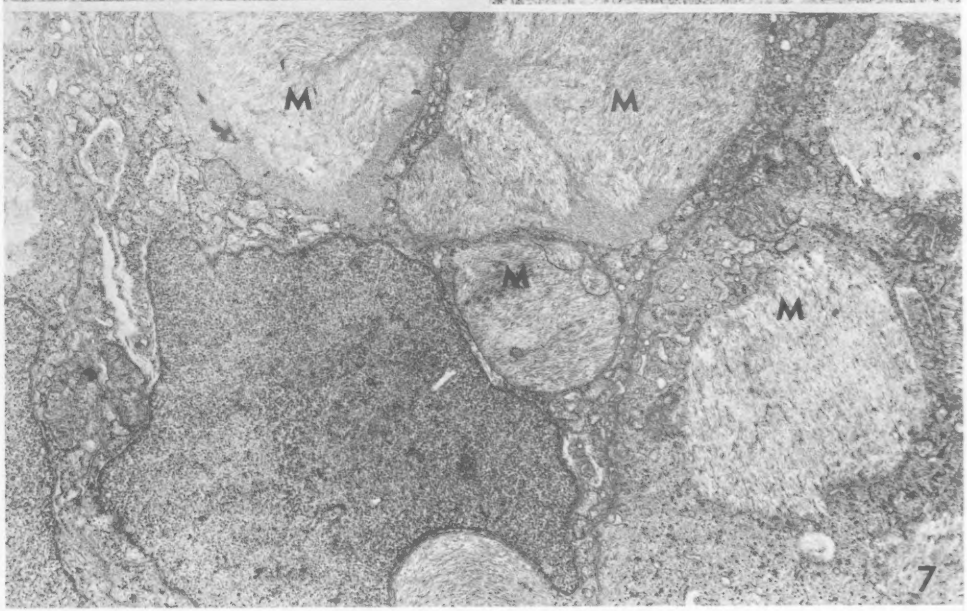

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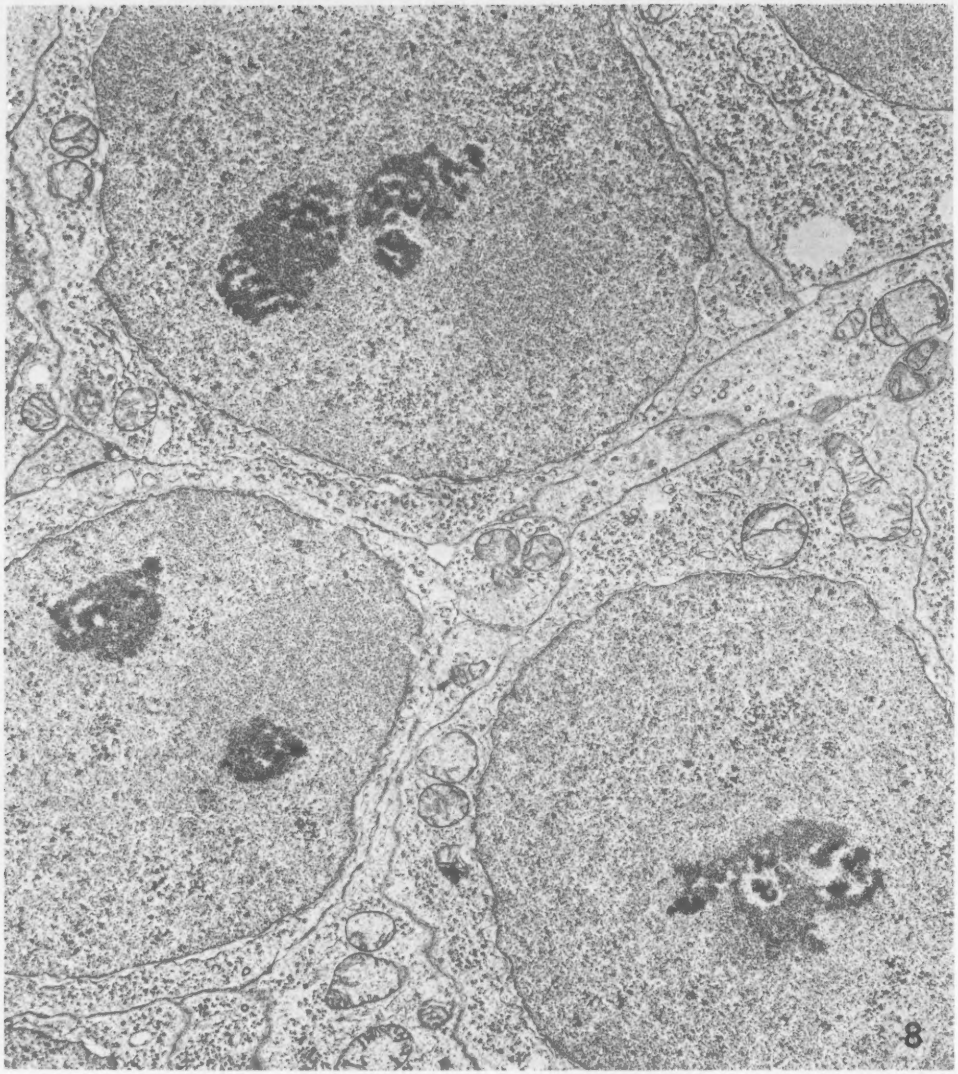

FIGURE 8.—Anaplastic carcinoma. Cells contain pleomorphic nucleoli. No desmosomes or evidence of adeno or squamous differentiation. Eight months after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 4200).

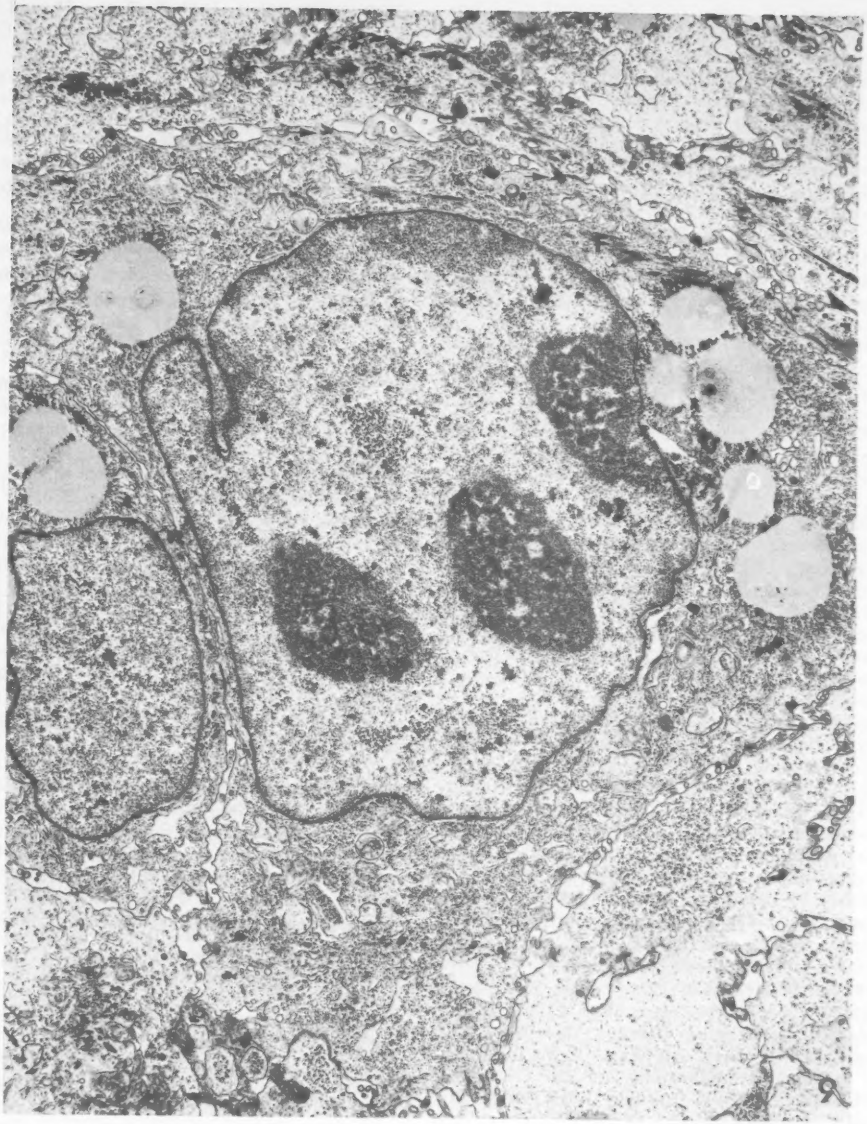

FIGURE 9.—Squamous cell carcinoma. Cells joined by desmosomes (→). Enlarged nucleus containing multiple nucleoli. Cytoplasmic fibrils (F) are present. Five months after last intratracheal instillation of BP-Fe_2O_3 (Group 1) (× 22,500).

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Observer Variability and Reliability in Lung Cancer Diagnosis

R. Yesner [1]

The Veterans' Administration Lung Cancer Chemotherapy Study Group (VALCCSG) was organized in 1957. An initial requirement for acceptance of patients to a study by this group was submission of positive histopathologic material to a panel of three pathologists (Drs. Raymond Yesner [chairman], Oscar Auerbach, and Bruno Gerstl). The same histologic slides were examined independently by each pathologist and each submitted a separate diagnosis. It soon became apparent that for results to be comparable, it was necessary to speak a common language, to devise an appropriate and useful nomenclature out of the welter of existing terms (1). One year after the organization of the VA group, the World Health Organization (WHO) agreed to establish an International Reference Center for Lung Cancer in Oslo. Drs. J. Delarue, H. Hamperl, L. Kreyberg, A. A. Liebow, R. W. Scarff, and E. Uehlinger established a tentative classification, which was immediately put into use by the Pathology Panel. That portion which dealt with epithelial tumors was as follows:

1. Epidermoid carcinomas
   (*a*) highly differentiated
   (*b*) moderately differentiated
   (*c*) slightly differentiated

Both the amount of keratinization and the proportion of keratinized cells were to be taken into account when considering the degree of keratinization.

2. Small cell anaplastic carcinomas
   (*a*) with oval cell structure (oat cell carcinomas)
   (*b*) with polygonal cell structure

Tumors transitional between categories 1 and 2 occur.

3. Adenocarcinomas
   (*a*) acinar
   (*b*) papillary
   } with or without mucus formation
   (*c*) tumors with a predominance of "large cells," some of which show gland formation and/or mucus production
4. Large cell undifferentiated carcinomas
5. Combined epidermoid carcinomas and adenocarcinomas
6. Bronchioloalveolar cell carcinomas
   (*a*) nonlocalized
   (*b*) localized
7. Carcinoid tumors
8. Tumors of mucous glands
   (*a*) cylindromas
   (*b*) muco-epidermoid tumors
   (*c*) other
9. Papillomas of the surface epithelium
   (*a*) epidermoid
   (*b*) epidermoid with goblet cells

Since the VALCCSG dealt only with carcinomas, only categories 1 through 6 were considered. The modified classification which was put into use was as follows:

1. Squamous cell carcinomas	10
(*a*) with abundant keratin	1*a*
(*b*) with intercellular bridges: epidermoid	1*b*
(*c*) without keratin or bridges: squamous	1*c*
2. Small cell undifferentiated carcinomas	20
(*a*) with oat cell structure	2*a*
(*b*) with polygonal cell structure	2*b*
3. Adenocarcinomas	30
(*a*) acinar	3*a*
(*b*) papillary	3*b*
(*c*) poorly differentiated	3*c*
4. Large cell undifferentiated carcinomas	40
5. Combined carcinomas	50

This modification is quite similar to the WHO classification, except that bronchioloalveolar carcinomas were included in section 3*b* since histologic experience indicated that they could not be differentiated. Experience with 2897 surgically removed specimens was published by the pathology panel (2). A total of 1120 specimens (38.7%) were obtained from metastatic or unknown sites. Squamous cell carcinomas comprised almost half (49.1%) of the total number of carcinomas. It is significant that almost two thirds (62.1%) of all centrally located tumors available to the bronchoscope were squamous cell carcinomas. The highly differentiated tumors (1*a*) were easily recog-

[1] Veterans' Administration Hospital, New Haven, Conn.

nized, the diagnosis being unanimous in 95.7% of the cases. The moderately differentiated tumors (1*b*) were almost as easily recognized, with unanimity being achieved in 91.4% of the cases. Together, 1*a* and 1*b* tumors comprised 57.5% of the squamous cell carcinomas and were designated epidermoid. On the other hand, the poorly differentiated group, 1*c*, which comprised 42.5% of the squamous cell group, achieved unanimity in only 46.6% of the cases, making this a highly unreliable category. It is not surprising, therefore, that whereas 50%–60% of 1*a* and 1*b* tumors were diagnosed by bronchial biopsy, only about one third of 1*c* tumors was obtained in this manner.

The small cell carcinoma group comprised 19.2% of the total. Of these, the oat cell group (2*a*) was diagnosed reliably, unanimity occurring in 84.0% of the cases. The relation of the oat cell to the squamous cell carcinomas was obvious in some specimens, and, as in the latter type, more than half of the oat cell carcinomas were found centrally in bronchial biopsy material. The polygonal group (2*b*) had poor reliability (34.4%) and only one fourth of them appeared on bronchial biopsy.

The adenocarcinomas comprised 15.8% of the total and appeared in less than 5% of the bronchial biopsies, confirming the peripheral origin of these tumors. With groups 3*a* and 3*b*, unanimity occurred in over 80% of the cases. Like other poorly differentiated tumors, 3*c* tumors were diagnosed unanimously in less than one half (42.5%) of the cases. Metastasis to scalene and clavicular lymph nodes occurred in 40% of this group.

The large cell undifferentiated carcinomas comprised 15.5% of the total, with unanimity occurring in only 10% of the group, the most frequent dissenting diagnosis being 1*c*. For this reason, categories 1*c* and 40 should probably be combined when large cell carcinomas (40) grow in sheets without demonstrable mucus or glands. The tumors in this group tend to be more central than category 30 and more peripheral than categories 10 and 20. It is a "waste-basket" group without clear objective criteria.

The combined carcinomas occurred in only 0.4% of all surgical material.

In December 1965, the Expert Committee of WHO met in Geneva and modified the original WHO classification. The pertinent portion of the final published classification (3) is as follows:

I. Epidermoid carcinomas

II. Small cell anaplastic carcinomas
  1. fusiform cell
  2. polygonal cell
  3. lymphocyte-like (oat cell)

III. Adenocarcinomas
  1. bronchogenic
    a. acinar
    b. papillary
    } with or without mucin formation
  2. bronchioloalveolar

IV. Large cell carcinomas
  1. solid tumors with mucin-like content
  2. solid tumors without mucin-like content
  3. giant cell carcinomas
  4. "clear" cell carcinomas

V. Combined epidermoid and adenocarcinomas

If this system were to be adopted, category I would be the equivalent of 1*a* and 1*b* in the VALCCSG classification and 1*c* would fall into the IV–2 group. Category II adds fusiform cell type to the small cell tumors, which have been listed as part of 2*a*. Category III moves bronchioloalveolar tumor from a separate category (6 in the original) to III–2, recognizing it as a papillary variety of adenocarcinoma; but the 3*c* group, poorly differentiated adenocarcinomas (solid tumors with mucin-like content), requiring mucin stains to reveal themselves, are removed from category III and placed in category IV (IV–1). This category is also enlarged to include IV–3 (giant cell carcinomas) and IV–4 (clear cell carcinomas). Many giant cell tumors may be identified by mucin stains as adenocarcinomas. We regard all carcinomas which produce clearly identified mucin within cellular cytoplasm (not stromal mucopolysaccharides) as adenocarcinomas (3*c*). Many clear cell carcinomas, given adequate material, may be identified as epidermoid carcinomas. Category V should be enlarged to include undifferentiated small cell carcinomas. It was decided not to alter the relatively simple classification of the VALCCSG in view of the long experience with this system, its proven practicality, and its close similarity to the WHO classification.

Having established the degree of reliability of various categories of lung cancer by percentage of unanimity of a three-man pathology panel, a definitive check on reliability was obtained by use of autopsy data on the same cases. In 1955, Walter and Pryce constructed a table based on studies done with surgical samples and necropsy samples (table 1). An astonishing difference in the number of squamous cell carcinomas was noted in the two series (60% in the surgical group and 20% in the necropsy group). Since they were based on different sets of patients, there existed the possibility of a sampling error. We therefore selected 617 patients for whom autopsies were available. The slides were coded and read independently by members of the panel. The results are shown in table 2.

The validity of this series of 617 surgical specimens is strengthened by the similarity of the breakdown of the histologic types to that encountered in the larger series of 2897 surgical specimens.

It is clear that in group 10, the epidermoid (1*a* and 1*b*) cancer percentages remained constant in the surgical-necropsy series (23.3% vs 23.5%), although increased keratinization was obvious. On the other hand, there was a sharp decline in the squamous cell tumors (1*c*) from 24.5% to 11.0%, resulting in a total decrease in group 10 from 47.8% to 34.5%. Simultaneously, group 30 rose from 16.0% to 25.6%, with the largest increase occurring in the poorly differentiated tumors (1*c*). It would appear from these figures that the diagnosis of poorly differentiated squamous cell carcinoma (1*c*) is an uncertain one, and that many are revealed by autopsy to be adenocarcinomas. Examination of the individual surgical cases diagnosed as 1*c* showed that at autopsy, 33% were substantiated as squamous cell, 28% were undifferentiated large cell, 21% were adenocarcinomas, 13% were undifferentiated small cell, and the rest were combined. There was a strong interchangeability between 1*c* and 40; about 50% of 1*c* cases fell into these two groups.

Further examination of the autopsy series showed that if the epidermoid cancers (1*a* and 1*b*) were segregated, half of these remained within the thorax without distant metastases. By contrast, over 90% of the small cell undifferentiated carcinomas showed widely disseminated metastases. The significance of careful histologic typing is obvious.

TABLE 1.—Histologic types determined surgically (207 patients) and by necropsy (159 patients)

Type	Surgical series (%)	Necropsy series (%)
Squamous cell	61.4	20.1
Oat cell	15.9	37.1
Adenocarcinoma	15.5	28.3
Polygonal cell	7.7	10.7

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TABLE 2.—Histologic types determined surgically and by autopsy for 617 patients with lung cancer

	Surgical series				Necropsy series			
	Type				Type			
Histologic group	*a*	*b*	*c*	Total	*a*	*b*	*c*	Total
10	7.1	16.2	24.5	47.8	13.6	9.9	11.0	34.5
20	13.9	5.2	—	19.1	19.0	3.7	—	23.2
30	7.8	2.4	5.8	16.0	10.4	3.9	10.0	25.6
40				16.0				14.7
50				1.0				2.0

The Epidemiology of Different Histologic Types of Bronchogenic Carcinoma [1]

Curtis C. Harris [2]

The incidence of the major histologic types of bronchogenic carcinoma is determined, in part, by exposure to carcinogenic agents. Cigarette smoke is clearly the primary cause of bronchogenic carcinoma. In fact, smoking is such a dominant factor that it is difficult to determine the influence of other environmental factors. It is equally difficult to determine the pattern of histologic types of bronchogenic carcinoma in the absence of smoking since the disease develops in few nonsmokers.

In table 1, the reported types of lung cancer in nonsmokers (1–5) are compared with those in a representative hospital series (6). Although these data are assembled from several reported series, the number of cases in the nonsmoking group is still small. In spite of this limitation, several generalizations can be made. (*a*) The same type of lung cancer develops in nonsmokers in both sexes. (*b*) Adenocarcinoma is the most common type, accounting for more than 50% of the cancer incidence. (*c*) While squamous cell carcinoma is uncommon, oat cell carcinoma and anaplastic carcinoma each account for less than 10% of the cancer incidence in both men and women.

The effect of smoking on the incidence of the common types of lung cancer is illustrated in table 2. The relative risk of occurrence of squamous cell carcinoma and oat cell carcinoma in smokers is greatly increased. To express Kreyberg's data (2) in a different way, 95% of all squamous cell carcinomas were attributable to cigarette smoking in that they would have been rarely seen if the Norwegians had all been nonsmokers. In addition, 90% of the oat cell carcinomas could be ascribed to smoking. It is against this backdrop that the occurrence of the various types of lung cancer in selected populations will be briefly considered.

[1] Presented at the Biostatistics Panel.

[2] Lung Cancer Branch, Carcinogenesis, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Md.

TABLE 1.—Distribution by type of lung cancers in a composite series of nonsmokers and a representative hospital series*

Type of cancer	Incidence (%)			
	Nonsmokers		All patients†	
	Men	Women	Men	Women
Squamous cell carcinoma	14	12	47	22
Oat cell carcinoma	4	4	17	11
Bronchiolar carcinoma	—	5	8	23
Adenocarcinoma	57	54	10	20
Large cell anaplastic carcinoma	8	8	17	19
Carcinoid	14	16	0.6	4
Other specific types	—	<1	1	2
Undifferentiated‡	4	2	—	—
Total No. of cases	51	274	1903	315

*Adapted from Berg (7).
†Representative hospital series (6).
‡Includes oat cell carcinoma and large cell anaplastic carcinoma.

TABLE 2.—Relative risk of occurrence of particular types of lung cancer in smokers as opposed to nonsmokers (age, 35–69 yrs)*

Type of cancer	Men	Women
Squamous cell carcinoma	25	12
Oat cell carcinoma	20	7
Adenocarcinoma	3	1.3
Bronchiolar carcinoma and carcinoid	1.0	1.1

*Adapted from Kreyberg (2).

The uranium miners of the Colorado plateau are one of the most interesting populations. Saccomanno et al (8) have described a possible synergistic effect between cigarette smoking and exposure to radon daughters. Interestingly, the most common type of lung cancer in these miners is oat cell carcinoma.

In table 3, the incidences of the types of lung cancer associated with specific occupational exposures to arsenic (9,10), nickel (9), chromium (9,12–14), hematite (15), and asbestos (9,11,16) are compared. In these series, squamous cell carcinomas have been most frequently associated with industrial exposure. However, the histologic characteristics and the pathogenesis of these tumors have been poorly documented. In addition, epidemiologic studies are complicated by the lack of correction for the smoking factor as well as changing fashions in the histologic classification of tumors. The synergism between cigarette smoking and occupational exposure to carcinogens has recently become evident (8,17,18).

Occupational exposure to mustard gas has caused an increased incidence of lung cancer (19). The median length of exposure to mustard gas was 7.4 years in these workers, while the median time between first exposure to the gas and diagnosis of cancer was 24.4 years. In comparison to mustard gas, the shortest exposure and development time for squamous cell carçinoma in Kreyberg's series (2) was 17 years; for "small cell anaplastic carcinoma," the shortest exposure and development time was 13 years. The mean exposure time to cigarette smoke for the development of the tumors mentioned above (Kreyberg's Group I) was approximately 35 years. As in cigarette smokers (table 1), the most common type of lung cancer reported in workers exposed to mustard gas was squamous cell carcinoma.

The major types of bronchogenic carcinoma are, for the most part, caused by exposure to *chemical* and *physical* carcinogens. Although oncogenic viruses cannot be excluded as a cause of bronchogenic carcinoma, there is little or no evidence for a viral etiologic agent. In addition to exposure to carcinogens, host factors (eg, immune and nutritional status) may determine the histologic type and biologic behavior of bronchogenic carcinomas.

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TABLE 3.—Histologic types of lung cancer associated with specific occupational exposure*

Type of cancer	Incidence (%) with exposure to—				
	Arsenic	Nickel	Chromium	Hematite	Asbestos
Squamous cell carcinoma	40	57	48	33	44
Oat cell carcinoma	13	43	16	60	6
Adenocarcinoma	7	—	24	—	25
Oat cell or anaplastic carcinoma†	40	—	—	—	24
Anaplastic	—	—	12	7	1

*Adapted from Berg (7).
†Hueper's grouping (9).

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Frequency of Residual and Metastatic Tumor in Patients Undergoing Curative Surgical Resection for Lung Cancer

Mary J. Matthews,[1] Suryabala Kanhouwa,[1] John Pickren,[2] and Dennis Robinette [3]

Early diagnosis of lung cancer followed by curative surgical resection should offer hope for a significant 5-year survival rate. At present, only 25% of all lung cancer patients are considered candidates for this mode of therapy when the disease is initially diagnosed, and less than one third of those who undergo a curative surgical procedure survive 5 years (1). Two questions may be raised concerning these facts: (*a*) how adequate are current procedures for staging of lung cancer, and (*b*) is there a predictable pattern of early metastases of lung cancer according to cell type which would warrant a more thorough and discriminant search for distant metastases? Little information beyond generalizations can be found in the literature on this subject. It seemed worthwhile to undertake a retrospective study of autopsy findings from patients who had curative lobectomies or pneumonectomies for lung cancer and who died within 1 month of surgery for whatever reason. The presence of residual, local, and/or distant metastatic disease in these patients might provide preliminary data and insight into these questions.

MATERIALS AND METHODS

Clinical, surgical, and autopsy data were reviewed on 140 patients in the Veterans' Administration Surgical Adjuvant Group (VASAG). These patients were considered to have had a curative surgical procedure for lung cancer and all died within a 30-day postoperative period. In each case, the surgeon felt that the tumor had been entirely encompassed and removed. Information was also reviewed on 62 similar patients who died within 30 days of a curative procedure at the Roswell Park Memorial Institute, Buffalo, New York, or who were in the Surgical Collaborative Adjuvant Study (RPMI–SCAS), maintained by Dr. Nelson Slack and affiliates. This report includes the 202 patients from both studies.

Information abstracted from the records included the primary site and size of the tumor; the presence or absence of blood vessel, lymph node, and pleural invasion; the presence of residual disease in soft tissues around the bronchial stump and in regional or mediastinal lymph nodes; and the presence or absence of distant metastases. In the original VASAG study, tumors were classified as adenocarcinomas, excluding bronchiolar carcinoma; epidermoid (squamous cell) carcinoma; and "other types," including large and small cell tumors. Small cell carcinomas were separated from this "other" category, according to the description and diagnoses of surgical pathology and autopsy microscopic data, so that the four major cell types could be examined.

RESULTS

Forty (28.5%) of the 140 patients in the VASAG series who were considered to have had a curative surgical procedure showed evidence of residual, local, or metastatic disease at autopsy (table 1). Almost one third of the patients with epidermoid carcinoma had persistent disease at autopsy and 60% of these patients had tumor limited to the bronchial stump and/or regional lymph nodes. Over 50% of the patients with small cell carcinoma had evidence of local or distant metastatic disease.

[1] National Cancer Institute-Veterans' Administration Medical Oncology Service, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

[2] Pathology Department, Roswell Park Memorial Institute, Buffalo, New York.

[3] National Research Council, Division of Medical Sciences, Washington, DC.

TABLE 1.—Incidence at autopsy of persistent malignant disease in 140 patients after curative surgical therapy for lung cancer (VASAG)

Cell type	No. of patients treated	No. of patients with—		
		Persistent disease	Residual/local disease only	Distant metastases
Epidermoid carcinoma	92	28 (30.6%)	17 (60%)	11
Adenocarcinoma	20	6	—	6
Large cell carcinoma	19	1	—	1
Small cell carcinoma	9	5	1	4
Total	140	40 (28.5%)	18	22

TABLE 2.—Incidence at autopsy of persistent malignant disease in 62 patients after curative surgical therapy for lung cancer (RPMI-SCAS)

Cell type	No. of patients treated	No. of patients with—		
		Persistent disease	Residual/local disease only	Distant metastases
Epidermoid carcinoma	39	16 (40%)	5	11
Adenocarcinoma	10	7	1	6
Large cell carcinoma	3	2	—	2
Small cell carcinoma	10	8	—	8
Total	62	33 (53%)	6	27

TABLE 3.—Incidence at autopsy of persistent disease in 202 patients after curative surgical therapy for lung cancer (VASAG and RPMI-SCAS)

Cell type	No. of patients treated	No. of patients with—		
		Persistent disease	Residual/local disease only	Distant metastases
Epidermoid carcinoma	131	44 (33%)	22 (50%)	22
Adenocarcinoma	30	13 (43%)	1	12
Large cell carcinoma	22	3 (14%)	—	3
Small cell carcinoma	19	13 (70%)	1	12
Total	202	73 (35%)	24	49

Curiously, only one of 19 patients with large cell carcinoma had evidence of metastatic disease in spite of the bulky size of the majority of these tumors at surgery.

Thirty-three (53%) of the 62 patients in the RPMI-SCAS group showed evidence of persistent disease at the time of autopsy (table 2). Over 40% of the patients operated on for epidermoid carcinoma had evidence of residual or metastatic disease. Sixty-six to eighty percent of the patients with other cell types had evidence of metastatic disease.

Table 3 summarizes the findings of the two series. Seventy-three (35%) of the 202 patients had evidence of persistent disease. A majority of the patients (131) had epidermoid carcinoma; 44 (33%) of these had persistent tumor identified at autopsy. Twenty-two had disease limited to the bronchial stump or the hilar or mediastinal lymph nodes. The remaining 22

TABLE 4.—Pattern of distant metastases according to cell type in 48 patients after curative surgical therapy for lung cancer (VASAG and RPMI-SCAS)

Site of metastasis	Epidermoid carcinoma	Adeno-carcinoma	Large cell carcinoma	Small cell carcinoma	Total
(No. of patients)	(22)	(12)	(3)	(12)	(49)
Adrenal glands	5	7	2	4	18
Liver	5	2	2	7	16
Brain	2	5	—	2	9
Kidney	3	1	3	2	9
Contralateral lung	3	—	2	1	6
Vertebra	—	3	1	1	5
Lymph nodes	6	4	1	6	17
Miscellaneous	4	3	1	2	10

patients had distant metastases. Thirteen of 30 patients with adenocarcinoma had persistent disease; 13 of 19 patients with small cell carcinoma had evidence of metastatic disease; and only three of 22 patients with large cell carcinoma had evidence of tumor at autopsy.

Seventy percent of the patients in the VASAG study and 50% of the patients in the RPMI–SCAS study had only one focus of tumor identified at autopsy. Forty-nine patients were found to have extrathoracic metastases. The distribution of the metastases according to cell type is presented in table 4. Although the figures are small, the epidermoid carcinomas appeared to metastasize with some frequency to the adrenals, liver, kidney, brain, and contralateral lung. Adenocarcinomas metastasized most frequently to the adrenals, brain, and bone; small cell carcinomas predominantly involved the liver and adrenals. The number of patients (three) with large cell carcinoma is too small to permit conclusions concerning predominant spread.

DISCUSSION

Sophisticated techniques for the preoperative evaluation of cardiopulmonary status; modern laboratory, anesthesia, and blood banking facilities; and new diagnostic procedures to identify extrapulmonary spread of lung cancer should progressively improve the dismal 5-year survival rate of patients who are considered surgical candidates. Mediastinoscopy is considered to be an effective method of demonstrating local mediastinal spread of lung cancer, precluding further surgical intervention. In 1966, Yashar (2) reported the results of transdiaphragmatic exploration of the upper abdomen at the time of surgery in 127 patients who were considered to have localized pulmonary cancer. Eighteen (14.9%) patients had metastatic disease in the liver. Undifferentiated carcinomas frequently demonstrated this phenomenon, while epidermoid carcinomas and adenocarcinomas metastasized to the liver less frequently. Hilar and mediastinal lymph node involvement were present in 90% of the patients with liver metastases. In 1968, Bell (3) attempted to identify occult abdominal metastases by performing laparotomies in 88 patients prior to definitive thoracic surgery for lung cancer. Seventeen (19.3%) patients had metastatic disease located predominantly in the liver or upper abdominal lymph nodes. The adrenal was identified as the site of metastasis in only one patient. No correlation could be made between cell type and site of metastases.

In 1968, Winstanley (4) investigated the cases of 79 patients who died within 1 month of curative surgical procedure for lung cancer. Twenty-one (26%) had metastases, predominantly involving the adrenals (nine patients), kidneys (six), liver (two), and brain (one). He was impressed that epidermoid carcinoma metastasized only half as frequently as other cell types and that the majority of metastases were essentially silent and probably undetect-

able by any present-day clinical or radiologic technique.

Hansen and Muggia (5) have recently reported the results of routine biopsies of the posterior iliac crest and liver in patients with limited and extensive pulmonary tumors. The liver was biopsied via peritoneoscopy allowing for direct visualization of much of the hepatic surface. Forty-six percent of the patients with small cell carcinoma had positive bone biopsies, in contrast to 18% of the patients with adenocarcinoma and 3.6% of the patients with epidermoid carcinoma. Liver biopsies were less helpful. Of a total of 47 patients, only four had positive biopsies. All four had small cell carcinoma, and three of the four were known to have had extensive disease.

In the present study, the following findings would appear to be of interest: (*a*) Of 202 patients who were thought to have had a curative surgical procedure, 73 (35%) had persistent tumor identified either as local spread or distant metastases within 1 month of definitive surgery. It is apparent that staging procedures for this portion of the cancer population were inadequate and that surgery was either insufficient or inappropriate without additional adjunctive therapy. (*b*) One hundred and thirty-one (65%) of the 202 patients had epidermoid carcinoma. Over one third of these patients (44) had tumor identified at autopsy, and in half of these (22) the tumor was localized to the bronchial stump or regional lymph nodes. In these cases the mediastinum was visualized and the tumor was either unrecognized or not examined at the time of surgery. Adjunctive therapy would possibly be helpful in such cases. (*c*) As might be expected, a much higher percentage of persistent disease was found in patients with small cell carcinoma (70%). Forty-three percent of the patients with adenocarcinoma had residual or metastatic disease. Only three of 22 patients with large cell carcinoma had metastatic disease, suggesting the possibility that some anaplastic cancers of the lung may possess a biologic behavior similar to the medullary carcinoma of the breast. (*d*) Seventy percent of the patients with persistent disease in the VASAG study and over 50% of the patients with persistent disease in the RPMI–SCAS study had only one focus of tumor identified at autopsy in a broad spectrum of organs. It would appear, therefore, that according to cell type there is no predictable site of early metastases in any individual patient. (*e*) Epidermoid carcinomas appear to metastasize less frequently than other cell types, but when they do metastasize, the most frequent sites appear to be the adrenals, kidneys, liver, contralateral lung, and brain. (*f*) Small cell carcinomas metastasize most frequently to the liver, adrenals, and abdominal lymph nodes. The data of Hansen and Muggia (5) strongly confirm that the bone marrow is an early site of metastases of this cell type. Lack of bone marrow involvement at autopsy may reflect inadequate sampling techniques rather than true noninvasion of this system. (*g*) Adenocarcinomas metastasize with frequency to the adrenals, brain, bone, and abdominal lymph nodes. (*h*) Large cell carcinomas share the metastatic behavior of all these cell types once the pulmonary vascular bed has been penetrated. (*i*) Scanning of the bone, liver, and brain is a significant part of the present-day armamentarium in suggesting metastatic or extensive disease. Routine bone marrow needle biopsy and aspirate from the posterior iliac crest should be included in the workup of patients with small cell carcinoma, adenocarcinoma, and large cell carcinoma. The development of discriminant techniques to identify occult metastases in the adrenals and kidneys would seem to be an important area of investigation, so that in the presence of such extensive disease, appropriate definitive and adjunctive therapy can be applied in a relatively early phase of the malignant process.

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Correlation of Histologic Types With Cell Kinetic Studies in Lung Cancer

Franco M. Muggia [1]

SUMMARY

Cell kinetic studies were performed in 28 patients with lung cancer. Intratumoral injections of tritiated thymidine were used to determine the thymidine labeling index (LI) following single or serial pulses. The highest initial values (median LI of 16.7%) and 48-hour LI values were obtained from patients with small cell carcinoma. In other cell types of bronchogenic carcinoma the LI was generally less, as was its rate of rise. These studies suggest that the fraction of proliferating cells differs among the various histologic types of lung cancer and accounts in part for their individual patterns of tumor growth and response to treatment.

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The various histologic cell types of lung cancer show differences in the frequency and pattern of spread of metastases. The current studies were undertaken to examine whether the cell population kinetic determinations using autoradiography and tritiated thymidine labeling would enable us to further delineate these differences.

MATERIAL AND METHODS

The studies were performed in 28 patients with histologically confirmed lung cancer evaluated at the NCI-VA Hospital Medical Oncology Service, Washington, DC. The methods employed (intralesional tritiated thymidine injection followed by biopsy sampling or aspiration) have been previously published (1,2). Similar techniques applicable to the study of tumor-replaced bone marrow have also been described (3).

The initial labeling index (LI), labeled mitoses curves, and the rise in LI following serial pulses have been determined through these techniques. Correlation between LIs of simultaneously determined sites, or between aspirate and biopsy determinations, has been good considering the nonrandom distribution of label in a solid tumor. The results include determinations where more than 1000 cells were counted; except in instances where the aspirate was unsatisfactory, the values represent results obtained by aspiration.

Because most patients were treated with chemotherapy immediately after the study, correlation with volume doubling times was not possible.

RESULTS

Small cell carcinoma.—Studies were most easily performed in these patients, relative to the other cell types; bone marrow invasion by tumor and other metastatic sites accessible for study were frequent, and tumor cells were aspirated with ease. Of the 12 patients studied, three had received prior radiotherapy to the primary lesion and one had received chemotherapy 1 month prior to the study.

The LIs in these 12 patients varied between 7.2% and 23.8%, with a median value of

[1] Divisions of Oncology and Hematology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY.

16.7%. The LIs following serial pulses at intervals of less than 12 hours rose to 55% and 44% in two patients, respectively, within 48 hours. A labeled mitoses curve in one patient yielded a duration of the DNA synthetic phase (T_s) of 18.8 hours; the mean intermitotic time (cell-cycle time, T_c) estimate was 64 hours. Correlation of clinical response with the LI was not possible because of the variable measures employed in the treatment of these patients. However, the patient with the highest LI (23.8%) showed a nearly complete response with a clinical regression of the tumor that lasted 10 months after receiving cyclophosphamide, methotrexate, and CCNU.[2] Five other patients showed an objective response to chemotherapy.

Three patients had followup LI determinations 5, 6, and 10 months after the initial determination. In two of the three, the LI was markedly reduced at the time of restudy.

Epidermoid carcinoma.—Six patients were studied on seven occasions. Two had previously received systemic chemotherapy and radiotherapy to the primary site; the remainder were previously untreated. Additional studies were attempted in three patients but central tumor necrosis in their nodules rendered the technique inapplicable. The LIs ranged between 0.9% and 9.8%, with a median of 2.5%. One patient was pulse-labeled serially every 12 hours for 96 hours. Biopsy of the specimen showed an LI of 40% confined to peripheral areas of the nodule; the center of the nodule was largely replaced by keratin and accounted for the inability to obtain specimens by aspiration. None of these patients showed a response to systemic chemotherapy.

Adenocarcinoma.—Three patients had LI determinations in peripheral nodules and two in tumor-replaced bone marrow. Only one of the three had received prior treatment. None had bronchoalveolar or papillary adenocarcinoma. The LIs varied between 2.6% and 4.9%. In one patient who was pulsed serially every 12 hours, the LI rose to 17.6% by 48 hours and to 22.1% by 84 hours. Response to chemotherapy was not observed in any of these patients.

Large cell undifferentiated carcinoma.—One patient with an undifferentiated cell type in the bone marrow (but with adenocarcinomatous elements found at postmortem examination) had an LI of 18.2%. A patient with clear cell carcinoma showed an LI determination of 10.4%, also in the tumor-replaced bone marrow. LIs of 12.3%, 5.7%, and 4.0% were obtained in three other patients from an inguinal lymph node, an abdominal wall nodule, and a replaced iliac bone marrow, respectively. All were untreated, except for two who had received radiotherapy to the primary site.

In the patient with the abdominal wall tumor, the volume doubling time was determined to be 17 days. The LI declined from 5.7% to 3.2% 2 months after the initial study. Serial pulse every 12 hours into this nodule showed a linear increase in LI to 43% by 96 hours.

Tumor regression was not seen in any of these patients after chemotherapy.

DISCUSSION

Intralesional studies have permitted evaluation of cell kinetic parameters in 28 patients with lung cancer. Analysis of the results by cell type indicates that median values of the LI are highest in small cell carcinoma. Moreover, the LI following serial labeling was higher by 48 hours in two of these patients than in patients with other cell types. On the other hand, the cell-cycle time and duration of T_s in one patient with small cell carcinoma were within the usual range of values reported for other solid tumors. These studies suggest that whereas cell-cycle times fall within relatively narrow ranges, wide differences may occur in the fraction of cells actively proliferating (growth fraction) among the various cell types of bronchogenic carcinoma. Determinations to estimate the growth fraction may therefore prove useful in outlining additional biologic differences in the growth of various bronchogenic cancers and in predicting responses to current chemotherapeutic approaches.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

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Data on Malignancy-Associated Changes in Oral and Bronchial Epithelial Cells in Sputum Specimens: Their Possible Utilization for Identification and Followup of High-Risk Groups

Franco Rilke and Silvana Pilotti [1,2]

SUMMARY

A total of 300 consecutive sputum specimens from 300 inpatients who had squamous and/or cylindrical cells with malignancy-associated changes type A (MAC-A) were evaluated. Retrospective analysis of the clinical data revealed the presence of malignant tumors in 292 patients and benign conditions in eight patients. In 140 patients, malignant tumor cells (MTC) were found in the sputum. Of these, 127 had a primary tumor in the lower respiratory tract and 13 had pulmonary metastases from other sites. Of the 152 patients with MAC-A-positive cells and no MTC in the sputum, 103 had primary carcinoma of the lungs and 49 had primary tumors in other sites. The strong coincidence (97.3%) of MAC-A-positive cells in sputum associated with malignant tumors either in the respiratory tract or elsewhere supports the significance of MAC as a diagnostic aid. The presence of MAC-A-positive cells in the absence of MTC indicates the need for further clinical search for possible occult or preclinical malignant tumors.

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Malignancy-associated changes (MAC), described for the first time by Nieburgs et al (1) in 1959, are nuclear alterations, which are consistent with malignancy, in otherwise normal-appearing cells of tissues adjacent to or distant from malignant tumors. Two types of MAC have been identified: one with an orderly nuclear structure (MAC-I) and the other with a disorderly chromatin pattern (2). The relationship of these two nuclear structures to the mitotic phase (3) and their identity with two of the three major nuclear types (4) led to the use of the terms MAC-A for MAC-I and MAC-C for MAC-II. MAC-C are more commonly found in tissues close to the malignant tumor (5), whereas MAC–A have been observed in several cell types of a high percentage of patients with malignant tumors in various distant sites (5,6).

This study is an extension of a previous investigation (7) which evaluated and interpreted the significance of differentiated squamous and cylindrical cells with MAC-A in smears of sputum specimens, with special reference to those without malignant tumor cells (MTC).

MATERIAL AND METHODS

We examined 300 consecutive sputum specimens from inpatients at this Institute. These specimens contained squamous cells of the oral epithelium, squamous cells of the upper respiratory tract, and/or cylindrical bronchial cells with MAC-A. MAC-C were not considered in

[1] Servizio di Anatomia Patologica, Instituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

[2] The excellent technical assistance of Miss Loredana Alasio and Miss Luisa Orcesi is gratefully acknowledged.

this study because of their less unequivocal recognition and limited significance. From fresh sputum specimens of spontaneous morning cough collected in 40% ethanol, four smears were prepared. These were fixed with surface spray and stained with the modified Papanicolaou technique (2). The cells were observed with 10x oculars and a Pl Apo 160x n.a. 1.40 oil immersion objective and were photographed with Kodakchrome II Professional KPA 135 film. Black and white photomicrographs were obtained from color dias.

MAC-A-positive cells were considered those with normal-appearing differentiated and mature cytoplasms, slightly increased nuclear-cytoplasmic ratios, well-preserved nuclei with intact membranes and nuclear structures characterized by deeply stained small chromocenters, and short curved chromatin bands, which demarcate round or slightly oval-shaped clear, but not optically empty, areas of fairly uniform size (figs 1 and 2).

The occasional appearance of larger chromocenters was considered compatible with type A structure; nucleoli had to be absent, especially in bronchial cells. For each specimen, the presence of ten squamous or cylindrical cells with definite unequivocal MAC-A was considered sufficient to label the case as MAC-positive.

In all cases, except for those with MTC in the first specimen, sputum examination was repeated. Those in which MTC appeared in successive specimens are listed in this study as MAC-A + MTC positive (*see* table 1).

After completion of the cytologic study, all data pertaining to the clinical history and present clinical, histologic, and radiologic findings were obtained retrospectively from a review of the patients' charts.

RESULTS

Of 300 sputum specimens with MAC-A-positive cells, 230 (76.6%) were from patients with primary tumors in the lower respiratory tract, 62 (20.7%) from patients with extrapulmonary primary tumors, and eight (2.7%) from patients with no evidence of malignant disease (table 2).

Of the first group, 103 (44.8%) sputa revealed MAC-A and no MTC, whereas 127 (55.2%) were positive for MTC; of the second group, 49 (79.0%) were MAC-A-positive and 13 (21.0%) were positive for both MAC-A and MTC.

In table 3 the modalities of diagnosis in the 230 cases of pulmonary cancer are given in detail. Five cases were stage T_x with positive cytologic test results without clinically recognizable primary tumor. A total of 182 had positive cytologic and/or histologic test results confirming the clinical and radiologic diagnosis. Histologic tests were carried out on either surgical specimens (lung, lobe, segment, wedge) or on transcutaneous puncture biopsy. Forty-two cases were recorded as clinically positive only, on the basis of roentgenograms, bronchography, lung-tumor scanning with $^{197}HgCl$, and, in a few instances, exploratory thoracotomy without histologic examination. At that time most of these 42 patients were already in an advanced stage of the disease and were considered inoperable. In most of the cases the first sputum specimen had been obtained before the start of therapy.

TABLE 1.—Occurrence of MTC in repeated sputum specimens from 230 patients with carcinoma of the lung

No. of patients with MAC-A + MTC noted in specimen No. —				Patients with MAC-A but no MTC	Total No. of patients
1	2	3	4		
97	21	7	2	103	230
42.2%	9.1%	3.0%	0.9%	44.8%	100.0%
	55.2%			44.8%	100.0%

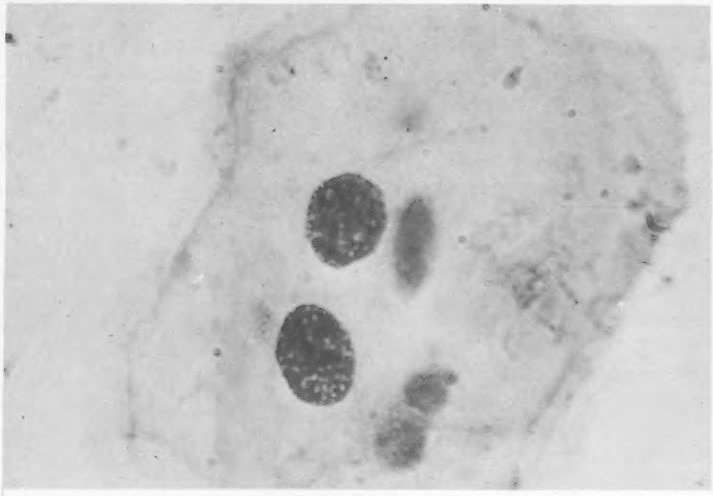

FIGURE 1.—Oral squamous epithelial cells with MAC-A. Hyperchromatic nuclei with clear circular areas of uniform size. (Papanicolaou's stain, × 1600)

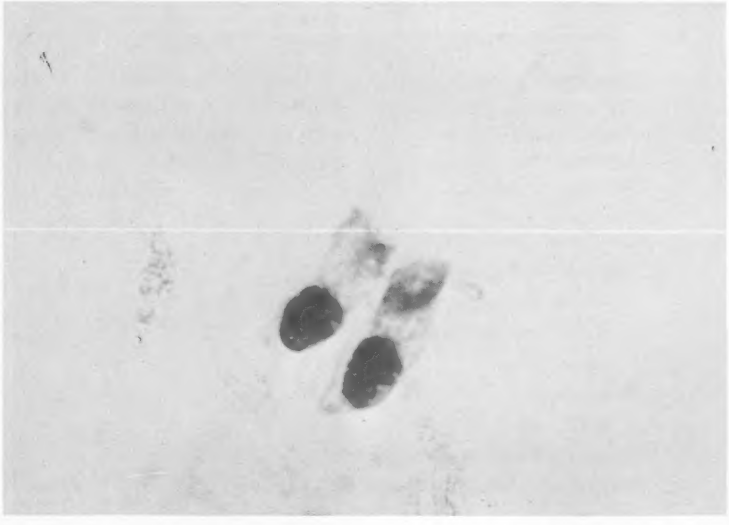

FIGURE 2.—Cylindrical cells of the bronchial lining with MAC-A. Slight increase of nuclear/cytoplasmic ratio, deeply stained chromatin demarcating clear circular areas. (Papanicolaou's stain, × 1600)

TABLE 2.—Final diagnosis in 300 consecutive patients with MAC-A and MAC-A + MTC in sputum specimens

Diagnosis	No. of patients with— MAC-A	MAC-A + MTC	Total (%)
Pulmonary primary malignant tumor	103	127	230 (76.6)
Extrapulmonary primary malignant tumor	49	13	62 (20.7)
No malignant tumor	8	—	8 (2.7)
Total	160	140	300 (100.0)

TABLE 3.—Modality of diagnosis in 230 patients with primary pulmonary malignant tumors with MAC-A in sputum

Modality of diagnosis	No. of patients	Percent
Cytologic	5	2.2
Cytologic + clinical	61	26.5
Cytologic + histologic	61	26.5
Histologic	61	26.5
Clinical	42	18.3
	230	100.0

MTC appeared in the sputum specimens of 127 of 230 patients with primary pulmonary tumors; in 97 patients, they were present in the first specimen, and in 30 patients MTC appeared in the second, third, or fourth sputum. Therefore, in these 30 patients the first smear should be considered negative for MTC and positive for MAC–A only. The 103 patients with persistently negative cytologic test results and MAC-A-positive cells had at least two repeated sputum examinations. As shown in table 1, 44.8% of 230 lung cancer patients had negative cytologic test results (two

TABLE 4.—Site and cell type of extrapulmonary primary malignant tumors with MAC-A and MAC-A + MTC in sputum

Site	Cell type	No. of patients with— MAC-A	MAC-A + MTC	Total
Upper respiratory tract	Squamous cell carcinoma	7	6	13
Breast	Carcinoma	7	1	8
Esophagus	Squamous cell carcinoma	4	—	4
Pleura	Mesothelioma	4	—	4
Kidney	Adenocarcinoma	1	1	2
Testis	Seminoma Embryonal carcinoma	2	—	2
Skin	Malignant melanoma	2	—	2
Ovary	Papillary carcinoma	1	—	1
Cervix	Squamous cell carcinoma	—	1	1
Stomach	Adenocarcinoma	1	—	1
Soft tissues	Fibrosarcoma	2	—	2
Lymph nodes	Hodgkin's disease	4	—	4
Lymph nodes	Malignant lymphoma, Histiocytic	4	1	5
Lymph nodes	Malignant lymphoma, Lymphocytic	2	1	3
Lung, metastatic	Carcinoma	2	2	4
Primary unknown	Squamous cell carcinoma	2	—	2
Primary unknown	Adenocarcinoma	2	—	2
Totals		49 (79.0%)	13 (21.0%)	62 (100.0%)

or more specimens examined); this percentage increases to 57.8% if the patients with MTC appearing in the second, third, and fourth smears were classified as negative.

Table 4 lists the sites and histologic types of extrapulmonary malignant tumors of 62 patients with positive MAC-A in sputum specimens. All of these patients had histologic confirmation of either a primary or a metastatic tumor. MTC were found in six of 13 patients with squamous cell carcinoma of the upper respiratory tract, one of eight patients with carcinoma of the breast, one of two patients with carcinoma of the kidney, and one patient with carcinoma of the cervix. In the first group a direct mixture of MTC with the sputum was anticipated; in the second group, MTC were derived from pulmonary metastases which were also recognized radiologically. Malignant histiocytes and lymphoid cells were present in the sputum of one of five patients with histiocytic lymphoma and in one of three patients with poorly differentiated lymphocytic lymphomas respectively. In two of four patients with pulmonary and extrapulmonary metastases of unknown primary epithelial cancer, MTC were present in the sputum.

In table 5, diagnosis, sex, and age are given for the eight patients with MAC-A in epithelial cells of sputum but without evidence of disease. All had been hospitalized with a provisional diagnosis of lung cancer and four (patients with intrathoracic neurinoma, cartilaginous hamartoma of the lung, pulmonary tuberculoma and silicosis, and sarcoidosis of the mediastinal lymph nodes) underwent surgery. Of the remaining four patients two had repeated thoracocenteses for pleural empyema and two had bronchiectasis.

DISCUSSION

Squamous cells with MAC-A in sputum specimens are readily identified by using the highest magnification of the light microscope, providing the material is well preserved and adequately fixed and stained. MAC-A-positive squamous cells may be either isolated or located within sheets among other MAC-A-negative cells. In bronchial cylindrical cells the basic nuclear A-type pattern is identical but somewhat more difficult to ascertain because of the more compact overall nuclear structure in comparison to squamous cells.

The results obtained indicate that of 300 consecutive sputa with MAC-A-positive cells examined in this laboratory, 292 were from patients with malignant tumors, of which 230 were located in the lower respiratory tract and 62 in other sites. In 57.8% of the patients with pulmonary malignant tumors the first sputum specimen was negative for MTC and repeated examinations were requested on the basis of the finding of MAC. The percentage of negative sputa decreased to 44.8% after two or more repetitions and MAC remained positive. In the group of 62 patients with extrapulmonary primary tumors the percentage of MTC in sputa was definitely lower (21%). In

TABLE 5.—Patient characteristics in 8 patients with nonmalignant conditions and MAC-A in sputum

Patient No.	Diagnosis	Sex	Age
1	Schwannoma, thorax	F	38
2	Hamartoma, lung	F	57
3	Sarcoidosis, lymph nodes	F	62
4	Tuberculoma + silicosis, lung	M	67
5	Bronchiectasis	M	62
6	Bronchiectasis	M	41
7	Empyema, pleura	M	36
8	Empyema, pleura	M	67

all, the diseases of 13 patients with pulmonary metastases proved by positive cytologic test results were confirmed radiologically. In the remaining 79% with MAC-A-positive cells and no MTC, the degree of radiologically demonstrable pulmonary involvement was variable from case to case; however, the majority of these patients had no proven pulmonary metastases.

The retrospective analysis of the charts of the patients, including the data on radiotherapy, chemotherapy, and other possible diseases of the respiratory system (such as asthma and emphysema), did not yield useful results as to a possible relationship to the presence of MAC-A-positive cells.

Patients with MAC-A-positive cells but no evidence of malignant tumor (2.7%) are still receiving periodic clinical control and six of them (7) have been followed for over 2 years. So far, sputum specimens have remained MAC-A positive.

As to the possible significance of MAC in cells which are often distant from the primary tumor (8), it has been stated that these changes may represent a systemic involvement of the host during the growth of the tumor (5). The five patients rated T_x with MAC-A-positive cells in oral epithelial cells indicate involvement prior to clinical manifestation of cancer. It has also been postulated that MAC may possibly appear prior to tumor growth (5). On the basis of this postulation it seems worthwhile that, during the cytologic study of sputum from patients with a high risk for lung cancer, MAC should also be recorded in order to gain further information on their biologic significance.

For practical clinical purposes it seems reasonable to utilize MAC findings as a diagnostic aid when MTC do not appear in specimens of patients with some clinical evidence of lung cancer.

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Reliability of Cytologic Diagnosis in Cancer of the Lung

John M. Lukeman [1]

SUMMARY

In 103 cases of primary cancer of the lung the diagnosis by sputum cytology was compared with that by histologic diagnosis. Cytologic studies were positive in 98% of the cases, however, the specificity of the cytologic diagnosis with regard to cell type was 75% correct. Analysis of the cases revealed that the poorly differentiated carcinomas and particularly the poorly differentiated adenocarcinomas which shed single cancer cells in sputum were the most difficult to classify correctly. Factors influencing accuracy and specificity of diagnoses are discussed. Illustrative examples are presented.

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In examining statistics from the past 18 years, it is apparent that in 1955 there were 27,000 deaths and in 1961 there were 39,000 deaths due to primary lung cancer in the United States. It is estimated that in 1973 more than 70,000 deaths will result from lung cancer. In a recent autopsy series one of every ten deaths was ascribed to primary cancer of the lung. The incidence of lung cancer as determined by autopsy at the turn of the century was approximately 3%–5%. This absolute increase in primary cancer of the lung is out of proportion to that which might be expected from the increment of increase in such diseases as pneumonia and heart disease. The increase in lung cancer is even more obvious when it is recognized that the incidence of cancer in other organs of the body has not changed appreciably.

The validity of the cytologic diagnosis of lung cancer is dependent upon many variables. Among these are the experience of the examiner, including his knowledge of the morphology of these tumors; the quality of the cytologic techniques utilized in smear preparation; and the lack of standard diagnostic criteria. A persistent problem affecting agreement in diagnosis is the failure by pathologists to agree upon or use a universally accepted cytologic or histologic classification of tumors.

The literature during the developmental years of exfoliative pulmonary cytology contains some interesting facts. In 1948, when pulmonary cytology was in its infancy, Liebow et al (1) reported on a series of 49 patients from whom an average of 3.2 specimens per patient had been collected. It was found that a correct "positive" cytologic diagnosis had been made in 42.8% of the sputa examined. The "positive" diagnoses were not subdivided into types of lung cancer such as squamous cell, adenocarcinoma, bronchioloalveolar, or undifferentiated small (oat) cell. Rather, the sputa were merely classified as containing or not containing malignant cells. In 1949, Watson et al (2) reviewed 235 cases of lung cancer. In each of these cases, three sputum samples were collected per patient, and the accuracy of positive diagnosis was 60%. The next year (1950) Woolner and McDonald (3) reviewed 147 patients from whom 1.6 specimens of sputum per patient had been collected. Cytologic collection and processing techniques had begun to improve and the accuracy of cytologic diagnosis

[1] Department of Anatomic Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

became more firmly established. Their results yielded a correct "positive" diagnosis in 68% of the sputa of patients with lung cancer. Ten years later, in 1960, Woolner (4) again reported a small series of 15 cases in which the number of sputum specimens per patient varied from two to 20. The accuracy of correct "positive" diagnoses in this series was 73%. In 1961, Meyer and Umiker (5) showed conclusively that cytologic diagnosis could not only be accurate and reliable but that a series of five sputum specimens usually represented adequate sampling of the bronchial tree. In their series of 158 cases they demonstrated conclusively that as the number of specimens per patient increased from one to five, the percent of positive cases reported increased proportionally from 78% to 94%. During the intervening 10 years not only had cytologic techniques improved but it had become apparent that specific histologic typing of lung cancer was indeed possible and accurate, on a cytologic basis at least, with regard to well-differentiated tumors.

The following classification of lung tumors is currently in use by the Cytology Service at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

Cytologic Classification of Primary Malignant Tumors

I. Squamous cell carcinoma
   1. Well-differentiated, keratinizing (fig 1, A and B)
   2. Moderately well-differentiated, nonkeratinizing (fig 2, A and B)
   3. Poorly differentiated (fig 3, A and B)

II. Squamous cell carcinoma in situ

III. Mixed adenosquamous cell carcinoma

IV. Undifferentiated small (oat) cell carcinoma (fig 4, A and B)

V. Adenocarcinoma
   1. Well-differentiated (fig 5, A and B)
   2. Poorly differentiated
   3. Bronchioloalveolar (fig 6, A, B, and C)

VI. Large cell undifferentiated (fig 7, A and B)

VII. Bronchial gland tumors
   1. Malignant mixed tumor
   2. Adenoid cystic carcinoma
   3. Mucoepidermoid carcinoma

VIII. Carcinoid

IX. Miscellaneous
   1. Lymphoma
   2. Sarcoma

In a retrospective study of 103 recent (1968–1970) cases of primary lung cancer taken from the files of the Section of Surgical Pathology where sputum cytology was also available, the sputa were examined for accuracy of cytologic diagnosis, for factors which would lead to erroneous diagnoses, and for false positive and negative diagnoses. These data are tabulated in table 1.

TABLE 1.—Retrospective analysis of 103 cases of lung cancer

No. of patients	Tissue type	Cytologic type
48	Squamous cell	Squamous cell
15	Adenocarcinoma	Adenocarcinoma
5	Undifferentiated small (oat) cell	Undifferentiated small (oat) cell
8	Unclassified malignancy	Unclassified malignancy
1	Adenosquamous cell	Adenosquamous cell
24	At variance with cytologic diagnosis	Positive with histologic variance
2	Adenocarcinoma	Inclusive (sample inadequate)
103 Total		

Analysis of the data in table 1 reveals the following:

1. Ninety-eight percent of the malignant cases were confirmed by histologic diagnosis.
2. Seventy-five percent of the histologically confirmed cases had a correct cytologic diagnosis.
3. In 2% of the cases the cytologic diagnosis was inconclusive.
4. There were no false negatives.
5. There were no false positives.

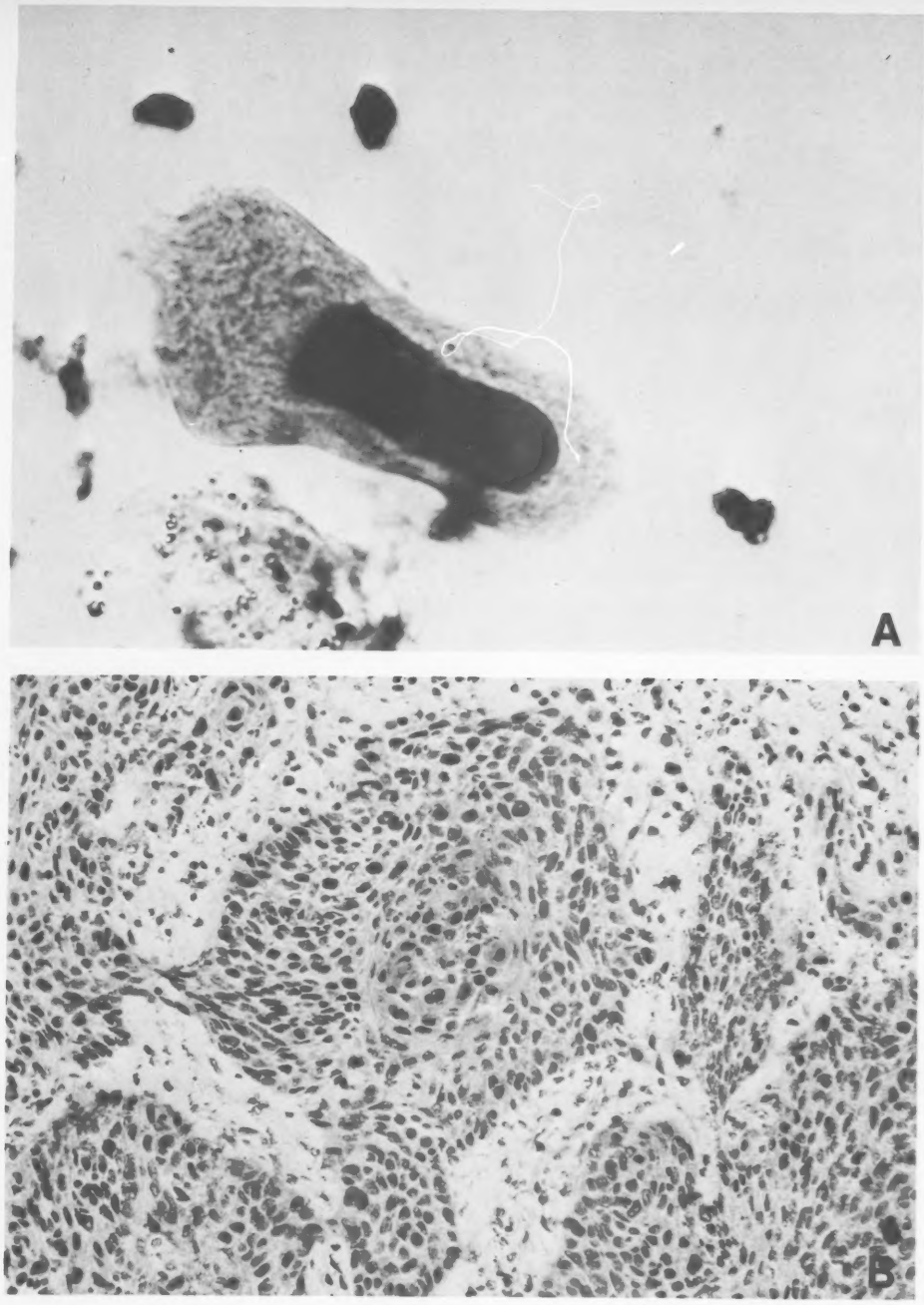


FIGURE 1.—(*A*) Well-differentiated keratinizing cell (Papanicolaou stain, × 1000). (*B*) Biopsy of tissue from the same case revealing cells in the tissue of identical morphology (hematoxylin and eosin stain, × 115).

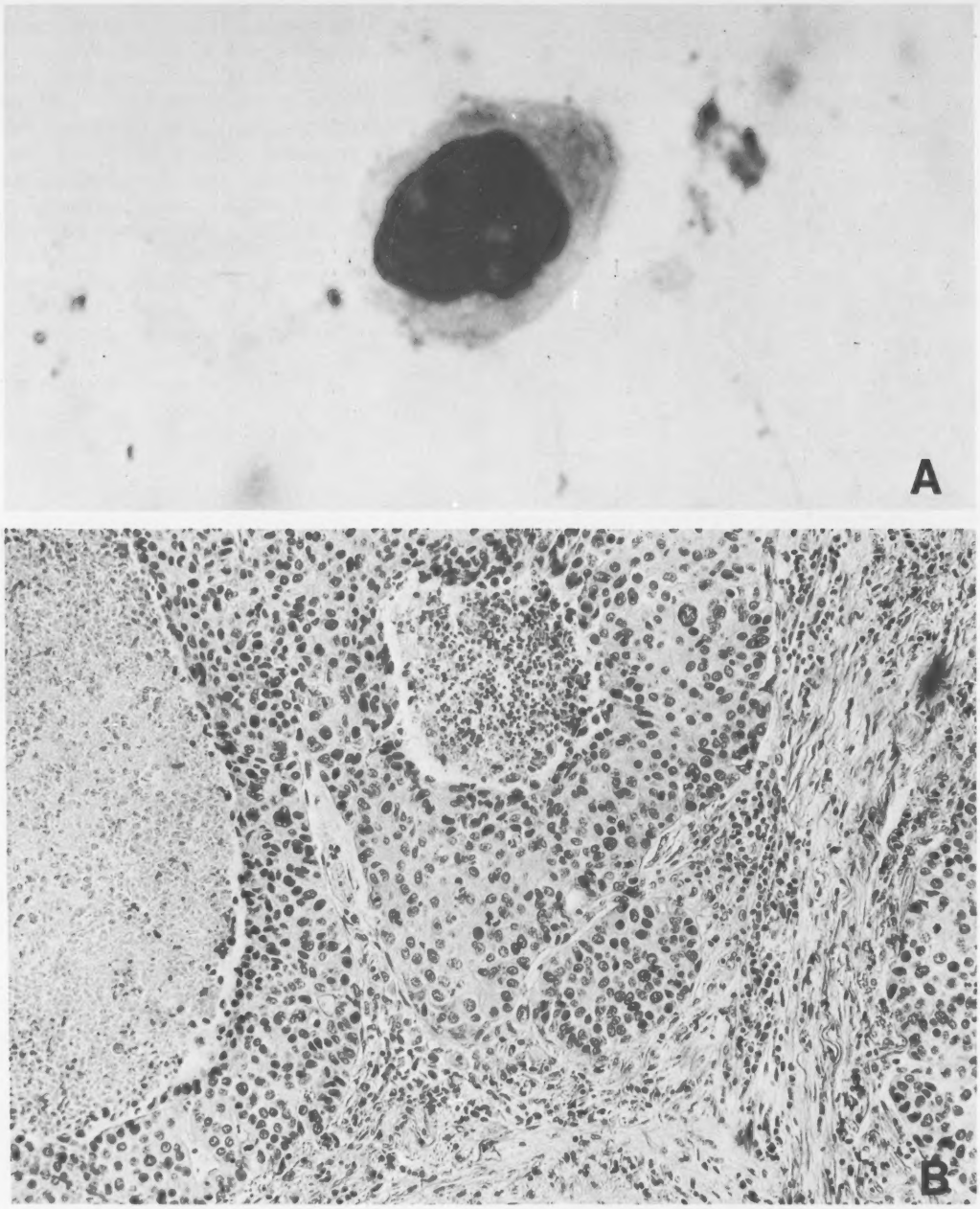


FIGURE 2.—(*A*) Moderately well-differentiated, nonkeratinizing squamous carcinoma cell (Papanicolaou stain, × 1200). (*B*) Biopsy of tissue from the same case showing similar cells and cytologic characteristics (hematoxylin and eosin stain, × 90).

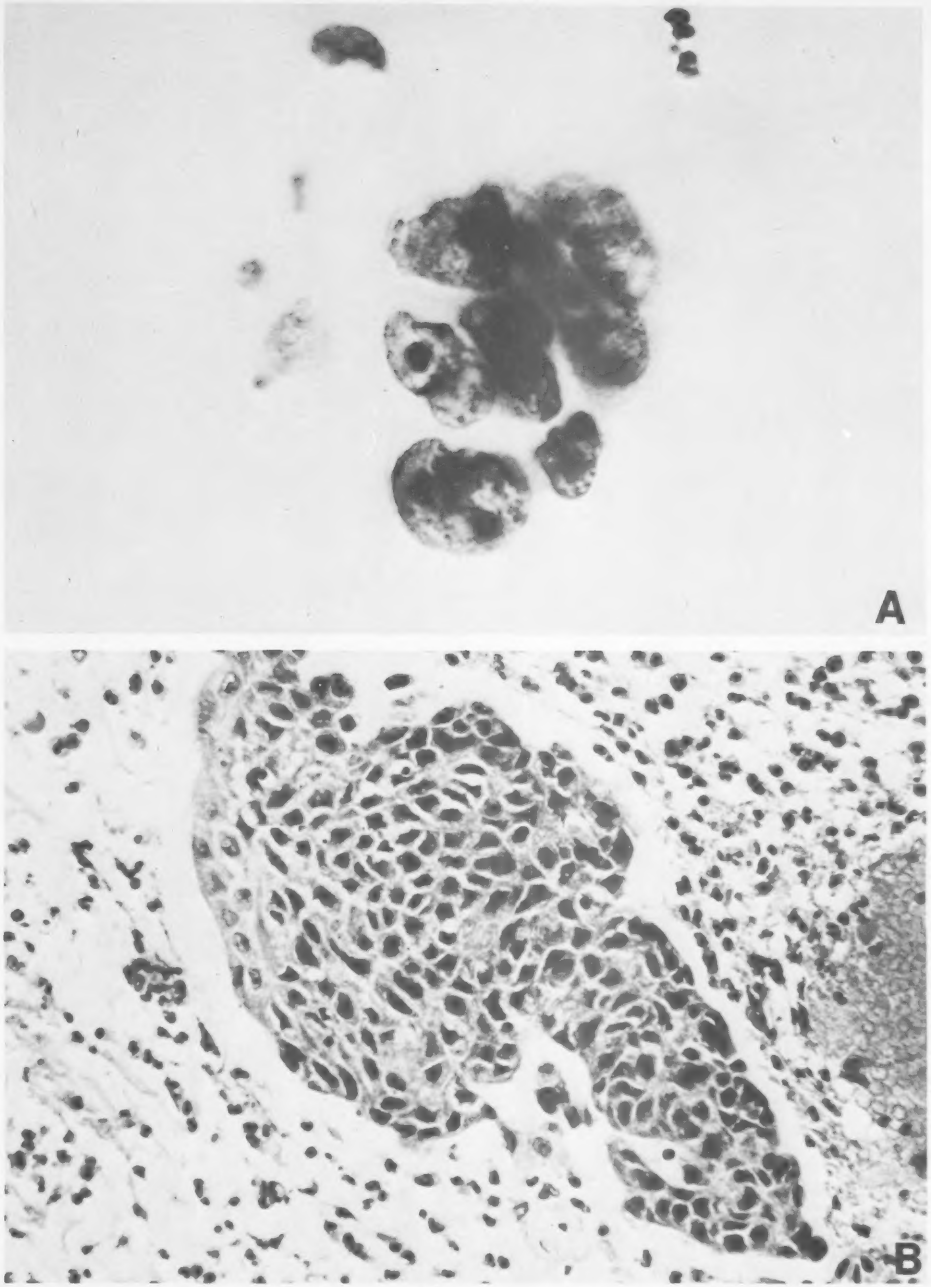


FIGURE 3.—(*A*) Cluster of poorly differentiated squamous carcinoma cells with few identifying criteria (Papanicolaou stain, × 800). (*B*) Tissue biopsy from the same case (hematoxylin and eosin stain, × 200).

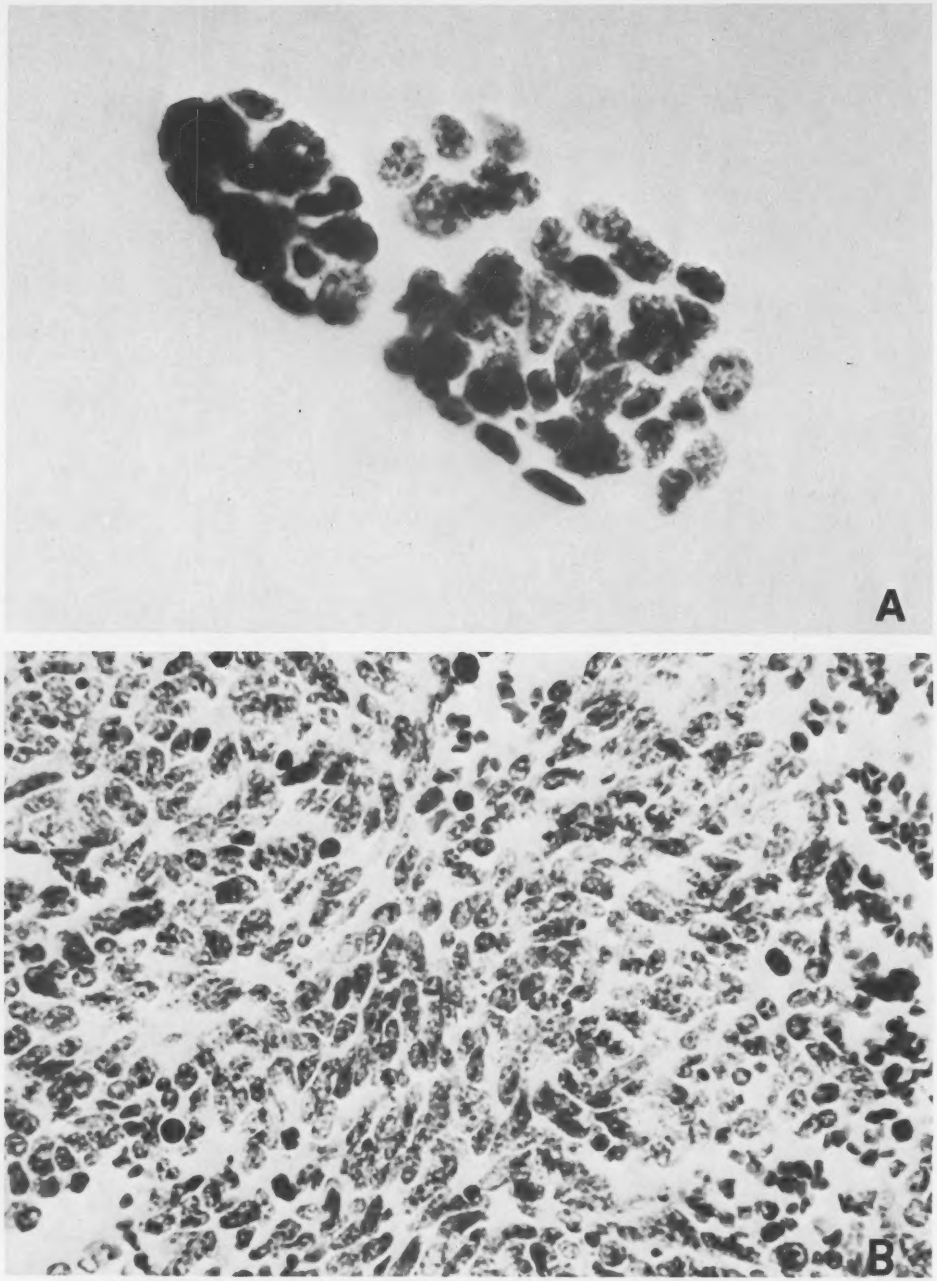
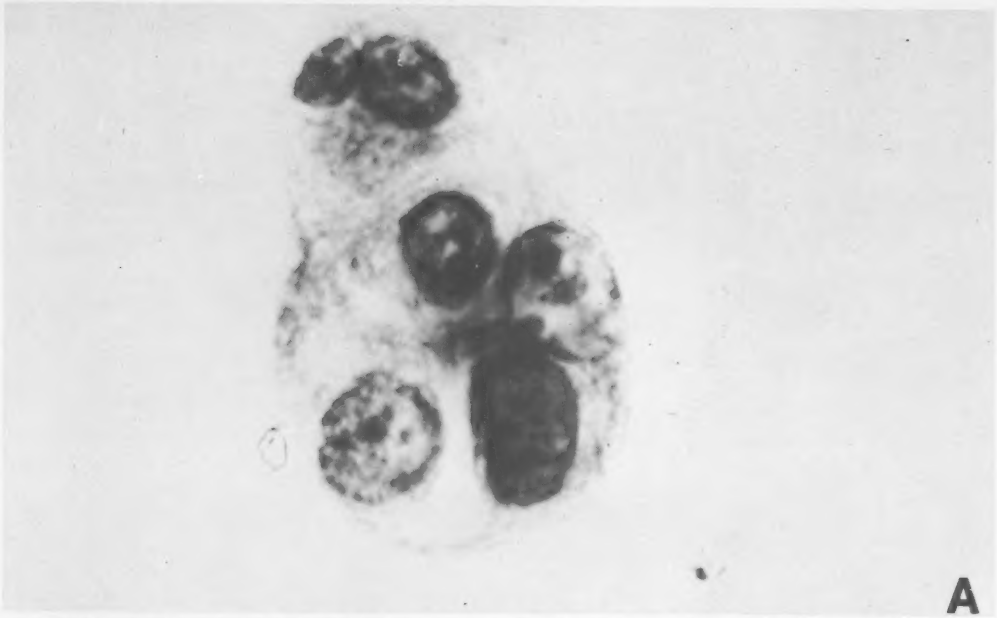


FIGURE 4.—(*A*) Undifferentiated exfoliated small cells with almost no visible cytoplasm in sputum (Papanicolaou stain, × 1200). (*B*) Tissue from the same case showing identical cells (hematoxylin and eosin stain, × 290).



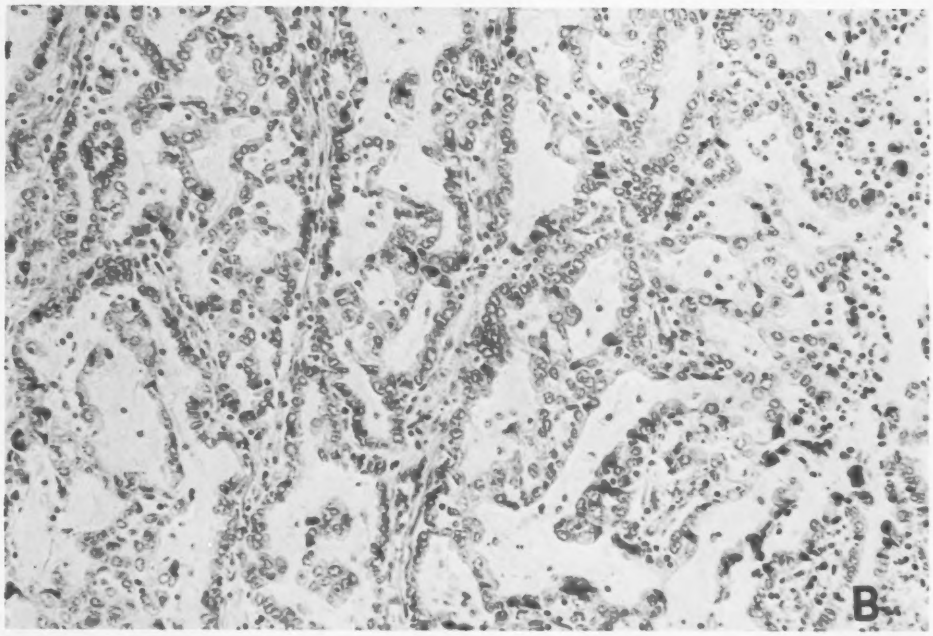
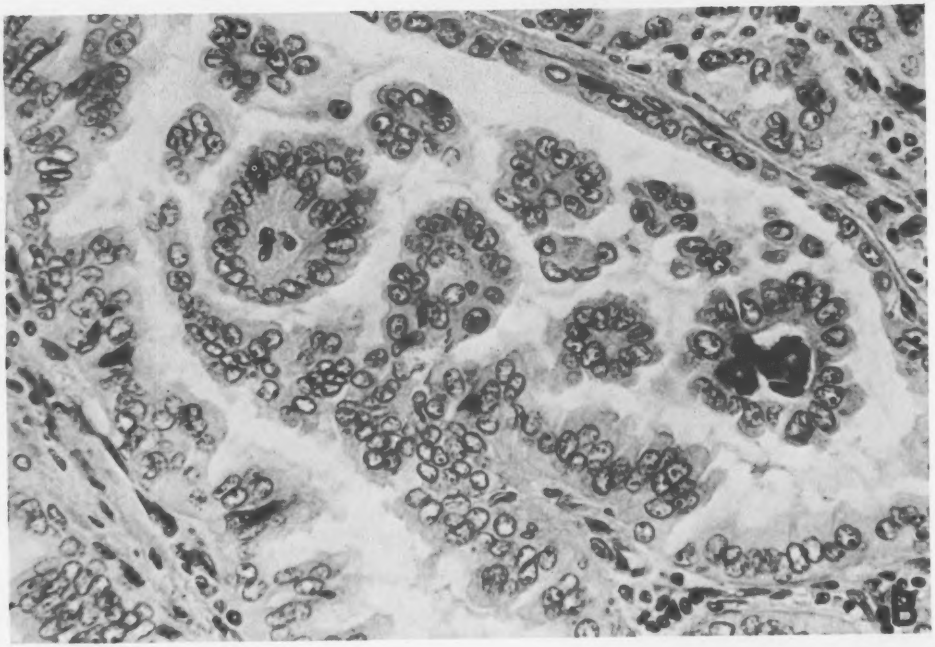


FIGURE 5.—(*A*) Characteristic aggregate of cells. The individual nuclei show malignant criteria: molding, pleomorphism, and a common community border (Papanicolaou stain, × 1150). (*B*) Tissue from the same tumor (hematoxylin and eosin stain, × 150).

A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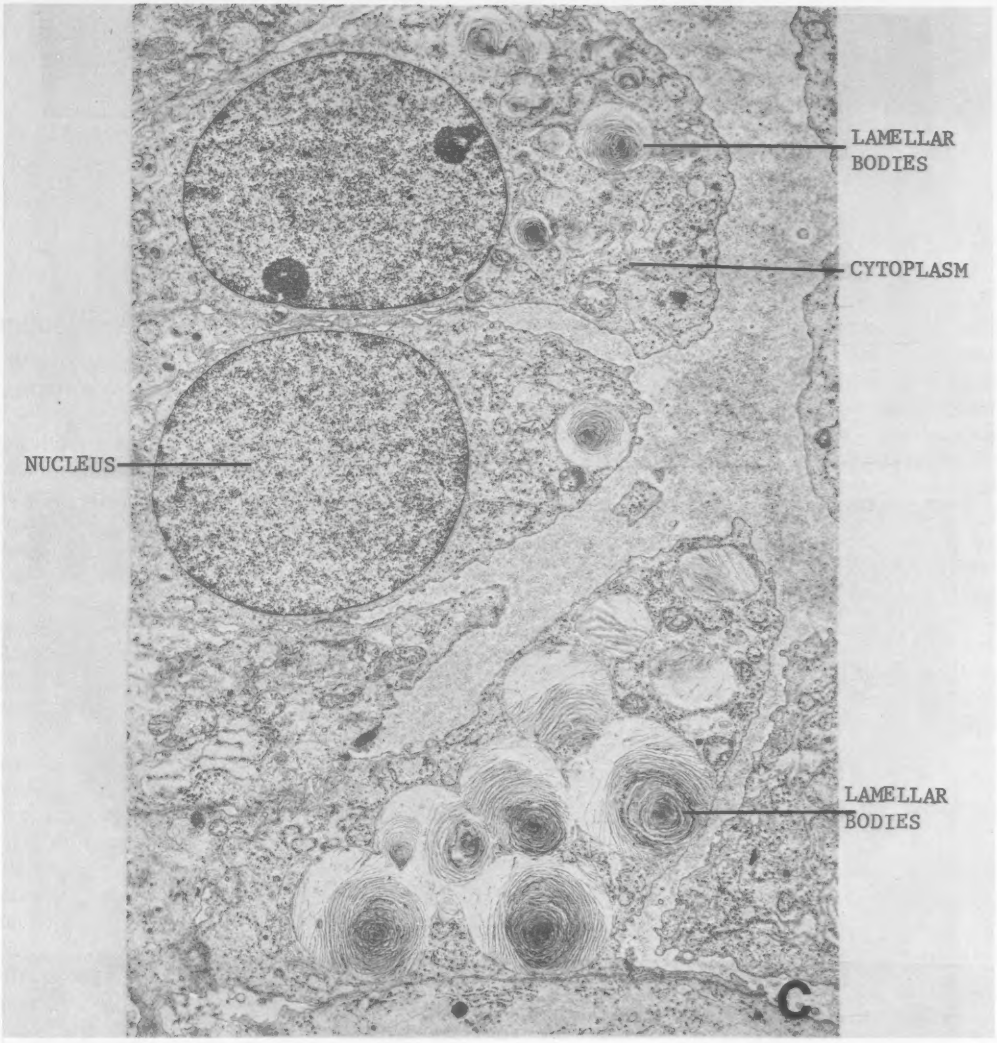

FIGURE 6.—(*A*) Bronchioloalveolar type adenocarcinoma. The nucleoli are characteristically large and prominent. Papillary fragments occur frequently (Papanicolaou stain, × 900). (*B*) Tissue with identical cellular characteristics (hematoxylin and eosin stain, × 225). (*C*) A low magnification photomicrograph taken with the electron microscope showing the characteristic lamellar bodies in the cytoplasm which differentiate this tumor from the non-alveolar cell adenocarcinoma (osmic acid stain, × 6.500).

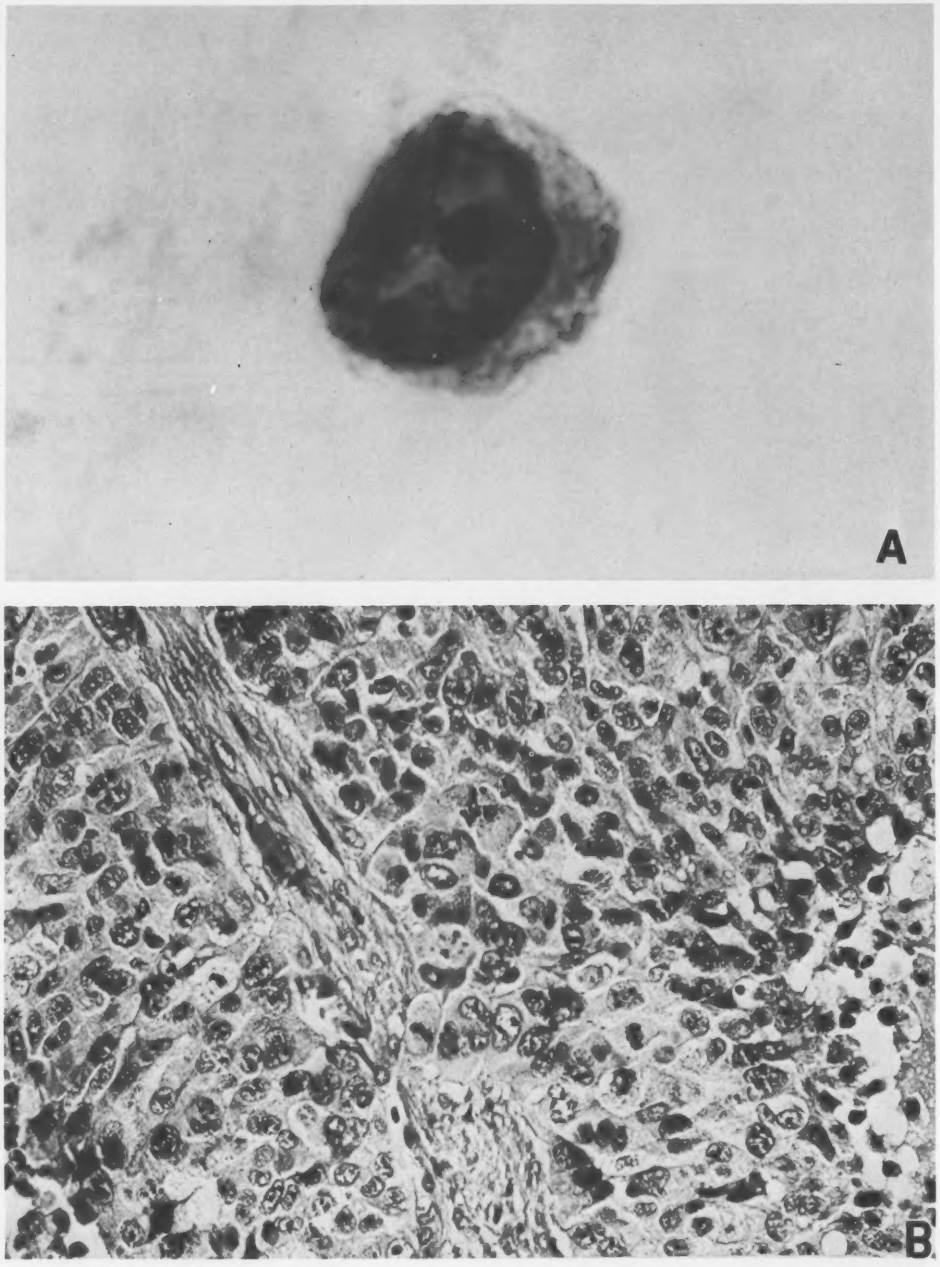

FIGURE 7.—(*A*) Large cell with single nucleus, two nucleoli, and poor diagnostic criteria for type designation but diagnostic as a malignant cell (Papanicolaou stain, × 1500). (*B*) Tissue from a similar case (hematoxylin and eosin stain, × 225).

TABLE 2.—Twenty-four cases in which the cytologic diagnoses were at variance with the positive histologic diagnoses

No. of patients	Tissue diagnosis	No. of patients	Cytologic diagnosis
22	Adenocarcinoma, poorly differentiated	5	Positive, unclassified
		16	Squamous cell, poorly differentiated
		1	Undifferentiated small (oat) cell
1	Squamous cell	1	Papillary adenocarcinoma
1	Bronchogenic undifferentiated (oat cell)	1	Squamous cell, poorly differentiated

DISCUSSION

When the 24 patients with malignant neoplasms whose cytologic diagnoses were at variance with the histologic diagnoses are examined, it becomes immediately apparent that 22 of 24 discrepancies occur in either poorly differentiated adenocarcinomas not forming acini, organoid structures, or cell aggregates, or in adenocarcinomas shedding single small cells. These discrepancies are tabulated in table 2.

In some of the cases where cytologic and histologic diagnoses were at variance, the histologic preparation frequently was extremely difficult to interpret. The diagnosis was often accompanied by a comment indicating that the tumor was poorly differentiated and difficult to classify. The above findings are suggestive of those reported by Lange and Hoeg (6), who found that the cytologic diagnosis of squamous cell carcinoma was correct in 94% of the cases. Adenocarcinoma was correct in 100% of the cases and there was an accuracy of 86% in the diagnosis of undifferentiated bronchogenic (oat cell) carcinoma. Classification of poorly differentiated (referred to as undifferentiated) squamous cell carcinoma was diagnosed accurately in 27% of the cases and accuracy of diagnosis of large cell undifferentiated carcinoma was correct in only 20% of the cases. It is apparent that precise identification of the undifferentiated or poorly differentiated tumors of the lung produce major diagnostic problems. Some of the discrepancies may be due to differences in interpretation since pathologists often utilize different criteria for the diagnosis of specific tumors. For example, some pathologists will accept a cancer as being squamous cell only if intercellular bridges, keratinization, and epithelial pearls are present. If these are not found, the tumor will be classified as an undifferentiated or poorly differentiated epithelial tumor. In cytologic specimens a factor that enters into the recognition and diagnosis of cell type is the state of cell preservation and the quality of the technique used in smear preparations. Where debris, mucus, and inflammation are present in quantity and where the sputum sample is scanty in its malignant cell population, poorly differentiated squamous cell carcinoma may be misinterpreted as poorly differentiated adenocarcinoma or undifferentiated carcinoma. Large cell undifferentiated carcinoma may be diagnosed as adenocarcinoma, nonkeratinizing squamous cell carcinoma, or undifferentiated carcinoma.

The following associated factors also influence the accuracy of cytologic diagnosis:

1. Tumor necrosis with cell degeneration
2. Granulomatous disease, especially tuberculosis
3. Lung abscess
4. Chemotherapy (busulfan),[2] immunosuppressive therapy, and radiation therapy
5. Infarcts
6. Lipid granuloma
7. Chronic organizing pneumonia
8. Tracheobronchitis

[2] Busulfan: NSC-750; CAS reg. No. 55-98-1; 1,4-butanediol, dimethanesulfonate.

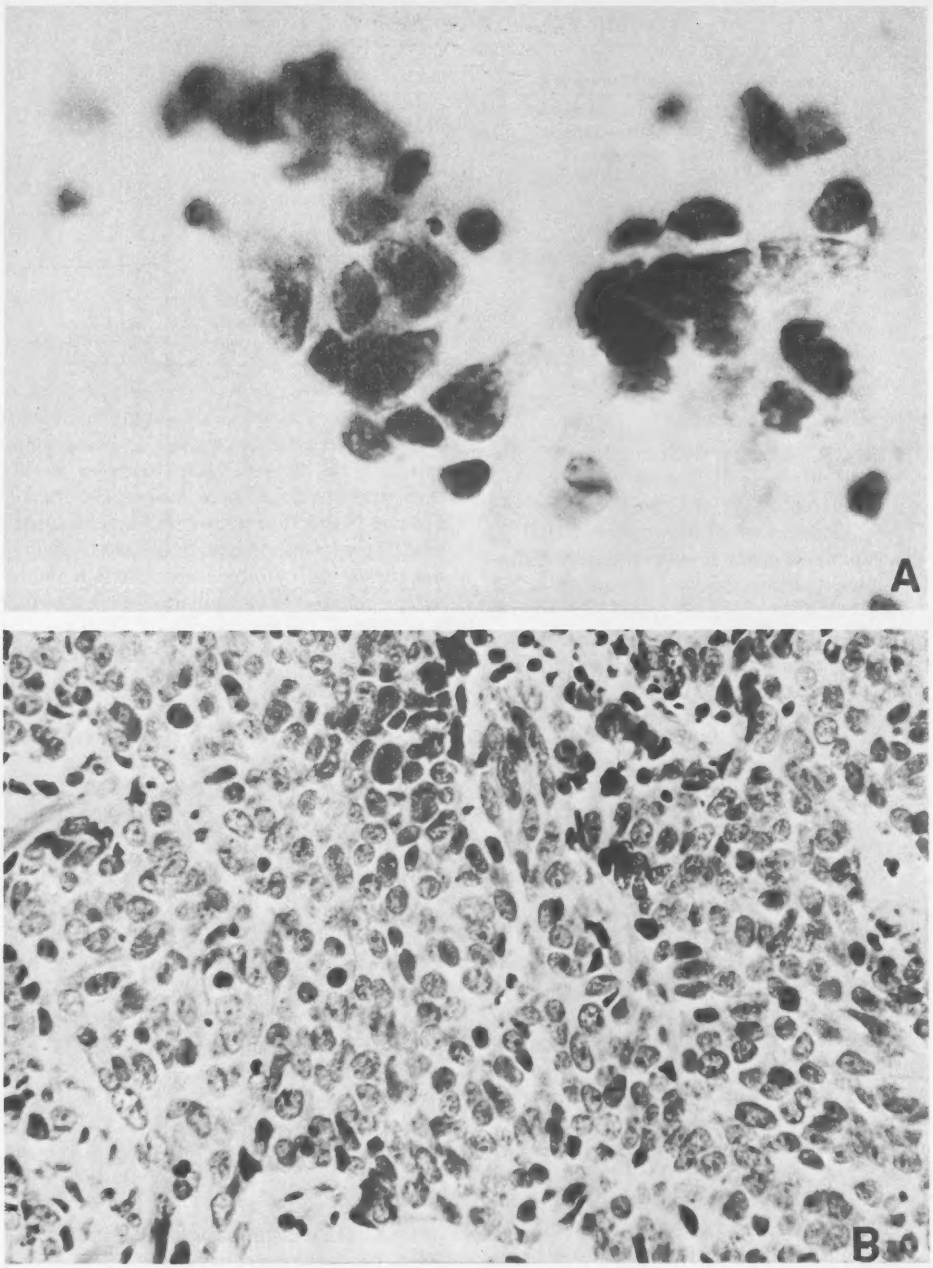

FIGURE 8.—(*A*) Undifferentiated small cell carcinoma. Aggregates of undifferentiated cells resembling oat cell carcinoma (Papanicolaou stain, × 1150). (*B*) Histology revealing a poorly differentiated adenocarcinoma (hematoxylin and eosin stain, × 250).

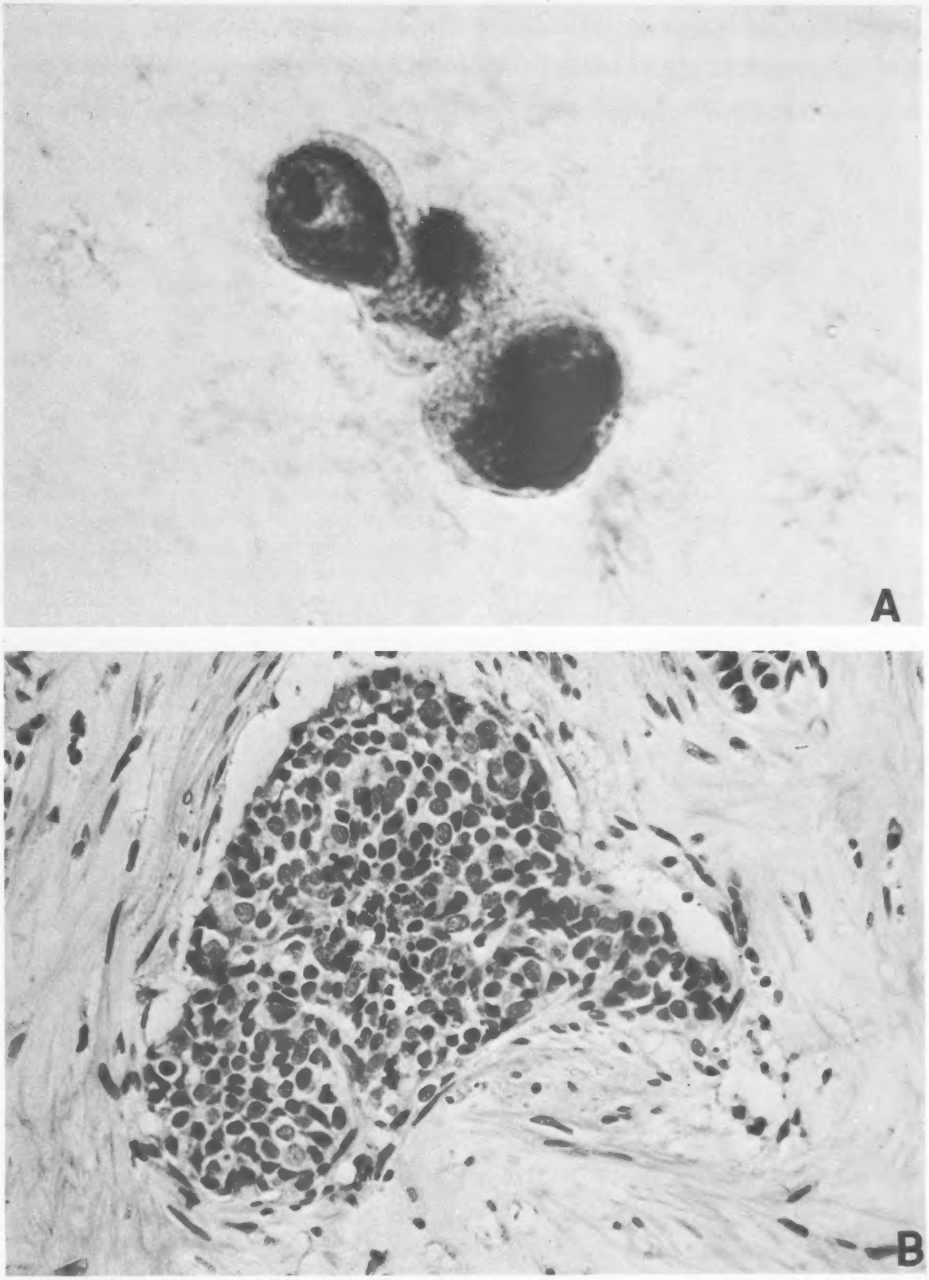

FIGURE 9.—(*A*) Adenocarcinoma, small aggregates of poorly differentiated cells (Papanicolaou stain, × 1000). (*B*) Tissue showing poorly differentiated squamous cell carcinoma (hematoxylin and eosin stain, × 300).

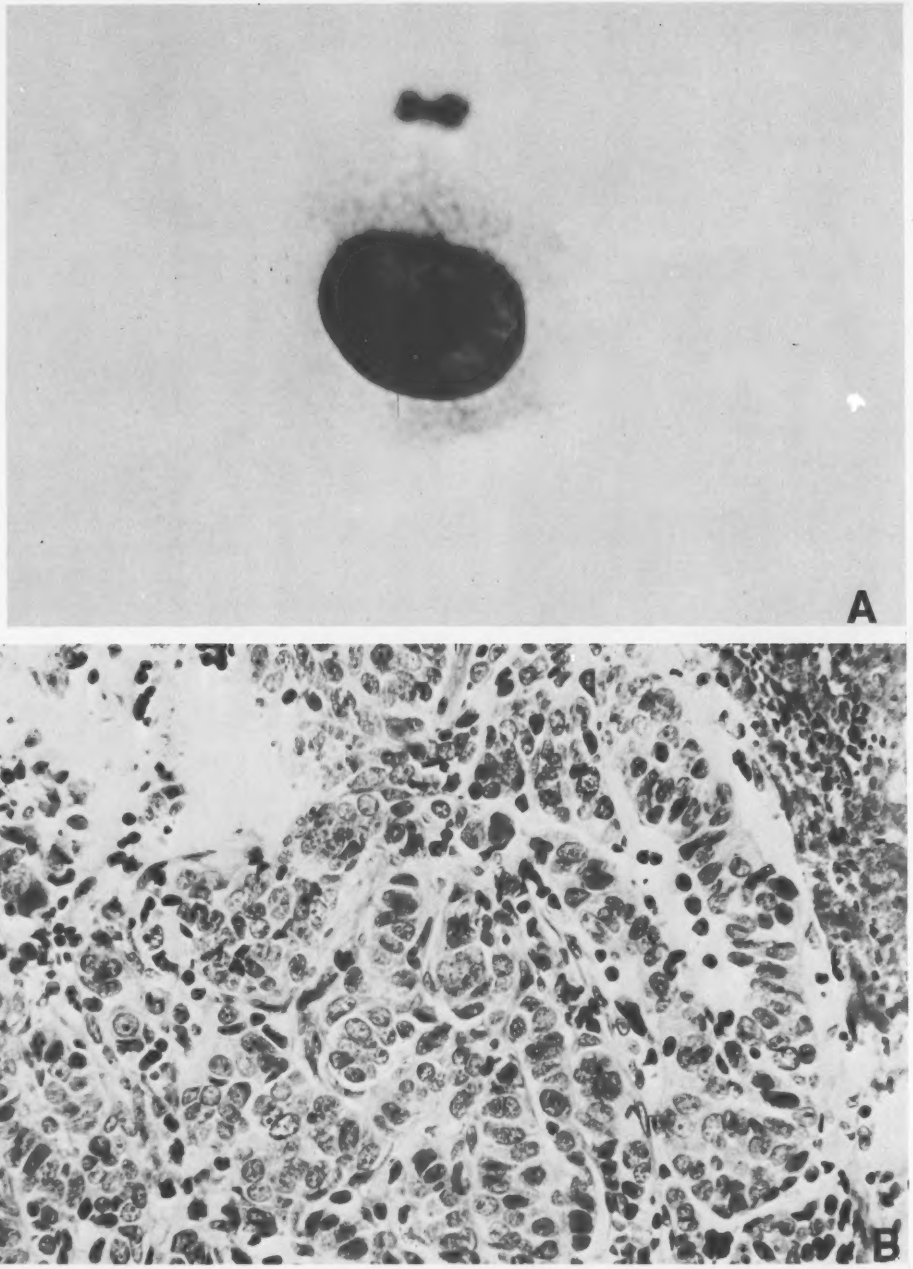

FIGURE 10.—(*A*) Squamous cell carcinoma with small cells poorly differentiated without characteristic community border of adenocarcinoma and tending to occur singularly (Papanicolaou stain, × 1150). (*B*) Tissue showing poorly differentiated adenocarcinoma (hematoxylin and eosin stain, × 225).

The following material demonstrates diagnostic and characteristic cell types of commonly occurring lung cancers together with their histologic counterparts. These are illustrated by three examples of "diagnostic problem cases" (figs 8, 9, and 10).

CHARACTERISTIC CELL TYPES

One hundred and three cases of lung cancer were reviewed, and diagnostic accuracy of the associated cytologic material was correlated. There were no false positive or false negative cases. Seven cases of cytologically characteristic lung cancer were presented as well as three cases which presented diagnostic problems cytologically and in which the cytologic classification differed from the histologic classification. Any preparation of the material examined may not be completely representative of the major portion of the tumor. In addition, factors such as tumor necrosis, inflammation, fixation distortion, therapeutic effect (busulfan), and atypical metaplasia may influence the judgment of the cytopathologist.

Lung cancer arises from cells of multiple potential. When many representative sections are examined, the pleomorphism of the neoplastic cells can be observed and the true cell type is sometimes exceedingly difficult to determine. Cases are encountered in which the initial cytologic or histologic diagnosis is changed after additional representative material is examined. Recent reports suggest that more cases of adenosquamous cell carcinoma are being recognized and that the incidence of this tumor is more frequent than was hitherto believed. This disease must become the primary target of medical research. It is mandatory that sufficient data and knowledge about biologic behavior of these tumors be gathered, that improved techniques for earlier detection be developed, and that more effective therapeutic regimens be instituted as soon as they have proved to be of value.

These facts point to the requirement for greater specificity in cytologic diagnosis and the need for correlative studies with electron microscopy.

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Survival Factors in Patients With Primary Lung Cancer Photofluorographically Detected

I. L. Stoloff [1,2]

From 1947 through 1970 the central X-ray unit of the Philadelphia Health Department detected 955 cases of histologically proved primary lung cancer. Nearly all patients have been followed and survival data have been analyzed. The 5-year survival rate from the date of roentgenographic detection of all cases was 12% and the 10-year survival rate was 10% (table 1). The factors which appear to be important in survival are sex, existence of symptoms at the time of tumor detection, first roentgenographic appearance of the tumor, bronchoscopic results, histologic type of tumor, and reason for the roentgenographic examination (compulsory or voluntary). There were 132 women with a 17% 5-year survival rate compared to 863 men with an 11% survival rate. When men and women were considered together there were 81 asymptomatic cases with a nodule and a 40% 5-year survival rate, 187 asymptomatic cases without a nodule with a 13% survival rate, 40 symptomatic cases with a nodule and a 12% survival rate, and 687 symptomatic cases without a nodule with an 8% survival rate.

The bronchoscopic results were most interesting. Of 125 patients with cancer in a main stem bronchus proved by biopsy there was only one survivor at 5 years, a survival rate of 0.8%. Of 135 patients with cancer in a peripheral bronchus proved by biopsy the 5-year survival rate was 9%. There were 327 patients in whom no tumor was seen inside a bronchus or in whom a biopsy failed to show cancer; their 5-year survival rate was 13%. The 241 patients with normal bronchoscopic findings had a 20% 5-year survival rate. Of 167 patients who did not have a bronchoscopic examination the survival rate was 10%.

In 431 patients with squamous cell cancer the 5-year survival rate was 12%, while the survival rates in those with undifferentiated carcinoma, adenocarcinoma, and other histologic types were 2.5%, 2%, and 2.5% respectively.

When the patients were classified according to whether they were required by law to have a roentgenogram (compulsory) or whether they came voluntarily, the differences in 5-year survival were significant. For example, among 289 men in the compulsory group and 574 in the voluntary group, the 5-year survival rates were 15% and 9% respectively (table 2). Of 55 women in the compulsory group and 80 women in the voluntary group the survival rates were 34% and 9% respectively (table 3). Using the Mantel-Haenszel test comparing compulsory and voluntary groups and adjusting for race-sex, smoking category, decade in which tumor was detected, and existence of symptoms

[1] Chest X-ray Detection Unit, Philadelphia Health Department, and Thomas Jefferson University, Philadelphia, Pa.

[2] Supported in part by contract 9-1393-649 to the Thomas Jefferson University from the Central Oncology Group.

TABLE 1.—Survival in patients with primary lung cancer detected by chest photofluorography: Philadelphia Health Department, 1947–1970

No. of years since diagnosis	Total No. of patients diagnosed	Patients surviving (%)
0–1	995	27
1–2	239	19
2–3	159	15
3–4	116	13
4–5	87	12
5–6	69	11
6–7	55	11
7–8	52	10
8–9	49	10
9–10	44	10
14–15	20	5
19–20	55	2

at time of detection, we found that the latter was the major factor influencing compulsory-voluntary differences.

The effects of bronchoscopic findings, histologic class, and presence of a solitary nodular cancer on compulsory-voluntary differences remain to be determined.

So far the results suggest that among those with lung cancer, survival varies among subgroups from a low of 0.8% in those with main stem bronchial tumors to a high of 59% in those with asymptomatic cancers first appearing as a solitary nodule in whom the results of bronchoscopic examination are normal. The 5-year survival rate in other groups is somewhere between these extremes.

It would appear that in planning treatment programs and in evaluating results we must consider these survival factors, and that those interested in nonsurgical therapy might start with a group of patients with main stem bronchial cancer (representing about 10% of all cancers) because of the very poor prognosis for this type of disease.

TABLE 2.—Survival in men

No. of years since diagnosis	Compulsory group		Voluntary group	
	Total No. of patients diagnosed	Patients surviving (%)	Total No. of patients diagnosed	Patients surviving (%)
0–1	289	33	574	23
1–2	90	23	116	16
2–3	58	18	76	12
3–4	41	16	56	11
4–5	33	15	42	9
5–6	29	13	31	8
6–7	24	13	25	8
7–8	21	12	25	8
8–9	20	11	22	8
9–10	16	11	22	8
19–20	1	1	2	2

TABLE 3.—Survival in women

No. of years since diagnosis	Compulsory group		Voluntary group	
	Total No. of patients diagnosed	Patients surviving (%)	Total No. of patients diagnosed	Patients surviving (%)
0–1	55	47	80	22
1–2	17	41	15	17
2–3	13	34	11	16
3–4	8	34	10	11
4–5	5	34	6	9
5–6	4	34	4	9
6–7	3	34	2	9
7–8	3	34	2	9
8–9	3	34	2	9
9–10	3	34	2	4
19–20	1	0		

Comparative Results of Right Pneumonectomy and Sleeve Lobectomy

A.-P. Naef [1] and J. Schmid de Grüneck [2,3]

Comparative results are reported on "radical" versus "economic" resection for right hilar carcinoma. This is a very limited aspect of the principal problem, ie, surgical treatment of bronchial carcinoma. This approach has been stimulated by the well-known drawbacks of total right pneumonectomy in elderly emphysematous cancer patients. The sacrifice of respiratory function and the high postoperative mortality rate may well be considered excessive. In cancer of the breast, minor surgical solutions have been advocated for cosmetic reasons. Similarly, it is certainly justified for vital reasons to look for alternative, economic operations in the treatment of bronchogenic carcinoma.

This investigation will indicate a few other pertinent conclusions important for the application and evaluation of surgical treatment of lung cancer whatever its location:

1. Long-term survival does not depend on the extent of a supposedly radical resection.
2. Mortality rates are lower and the function and quality of survival are better after economic resections.

PATIENTS

Looking at the distressing overall results of our series it is important to emphasize several points:

1. All our patients had far-advanced (stage 3) bronchial carcinoma.
2. This investigation has not yet been completed and the results may improve with time and with the inclusion of survival figures of the patients still living.
3. Right hilar carcinoma is the form of lung cancer with the poorest prognosis and its surgical treatment, whatever the technical procedure, will yield the most unfavorable results as compared to carcinoma treated by lobectomies or left pneumonectomies.
4. Surgery is generally not performed for oat cell carcinoma, but six of the 47 cases in our study, not diagnosed before operation, were of this type. These patients were not excluded from the study.
5. Patient referral in a highly specialized hospital is not geographical and does not represent the natural case variety, but rather a selection of unfavorable cases sent to a specialized team. Economic surgery may be the ideal treatment for highly selected localized bronchial carcinomas (1,2) or, as a comparison, for extremely well-localized breast carcinomas. On the contrary, our patients had mostly various types of extensive right hilar carcinomas (stage 3). These cases are often inoperable by total pneumonectomy for functional reasons and the only possible surgical approach is sleeve lobectomy. Sleeve lobectomy is defined as a lobectomy combined with sleeve resection-anastomosis of the invaded mainstem bronchus (3, 4).

TECHNIQUE

Surgical technique is of limited importance in this investigation except for its influence on serious complications and the disadvantages of the method. The economic resection of a massive hilar carcinoma is always technically difficult, and is performed with patience and determination to prevent a high-risk pneumonectomy or a useless exploratory thoracotomy. Sleeve resection of the right upper lobe with

[1] Associate Professor for Thoracic Surgery, University of Geneva, Switzerland.
[2] Department of Surgery, Hôpital d'Yverdon, Switzerland.
[3] *Reprint requests to:* A.-P. Naef, MD, Yverdon Hospital, 1400, Yverdon, Switzerland.

or without the middle lobe is the classical operation.

Re-implantation of the upper lobe-bronchus to the carina after lower and middle sleeve bilobectomy may be useful but seems to carry the risk of anastomotic stenosis. Separate chromic catgut sutures tied outside the bronchial lumen have not been followed by fistula or suture disruption.

Suppurative bronchitis may be the cause of all complications (bronchial necrosis, perianastomotic abscess, fistula, stricture, hemorrhage) and should be cured before operation. Cortisone may be helpful in preventing bronchorrhea and thus suture trauma by repeated coughing, but its effects on anastomotic healing may be unfavorable.

Two major complications which we suspect to be relatively frequent and related to bronchial infection will be studied. They are (*a*) late massive hemoptysis (virulent infection and nonresorbable suture material may be an etiologic factor), and (*b*) bronchial necrosis (leading to fistula or stricture). We suspect that these complications may be of importance for the following reasons. One of our patients has died at home 4 weeks after leaving the hospital, apparently with massive hemoptysis. He was not seen by a specialized physician at that time and no autopsy was performed. One patient who died in the hospital had a bronchoscopy just before death, by aspiration-pneumonia. The bronchial mucosa seemed necrotic even though there was no suture disruption. One other patient had subtotal anastomotic stenosis after an unexplained febrile postoperative course.

RESULTS

Because of the number of patients in our study (47), sound statistical conclusions may be made. The striking observation is a 50% survival rate at 1 year for the patients receiving sleeve resections compared to a 75% mortality rate in less than 1 year for the patients receiving pneumonectomy (table 1). Without mentioning the difference in quality of survival, the absolute quantitative survival time seems to be statistically significant. Detailed results of the two groups follow:

After pneumonectomy (29 patients) only seven patients lived more than 1 year; the four "longest" survivors lived just 12, 15, 20, and 25 months after operation. Five patients lived more than 6 months; three of them are still living. Seventeen patients (five postoperative deaths included) lived less than 6 months with a poor quality survival. Operative mortality was 17% (five patients).

After sleeve lobectomy (18 patients) nine patients passed the 1-year limit; the four longest survivors are doing well 14, 17, 21, and 41 months after the operation. Nine patients have survived less than 12 months up to now, but three recently treated patients are still alive with a good prognosis. There was only one operative death (5.5%). The quality of survival is strikingly better (patients are working, gaining weight, and living normal lives) in 13 cases compared to only five poor quality survivors.

SUMMARY AND CONCLUSIONS

The results of this investigation are still provisional but a statistical analysis seems to confirm the following facts. The prognosis of right hilar carcinoma is extremely serious. Unless other means of treatment prove more satisfactory, surgery seems justified by the occasional unpredictable "cure" of a "lucky" patient and the favorable palliative result in the majority of cases. A major advantage of sleeve lobectomy is the low mortality rate. Right pneumonectomy, at all costs, produces a high mortality rate, a great risk of respiratory insufficiency, and a dubious prognosis. Le Roux has published a mortality of 16.6% for right pneumonectomy (5).

Patients undergoing sleeve lobectomy will have at least the same prognosis but this procedure may be preferable to pneumonectomy for the following reasons: (*a*) better functional results; (*b*) better long-term survival; and (*c*) better quality of life.

The final results will depend on the aggressiveness of the cancer and the immunologic resistance of the patient. Therefore, surgeons must be modest in the evaluation of their results, but should aim to achieve the best pos-

TABLE 1.—Late results of right pneumonectomy or bronchial resection

Operation	No. of patients	Survival >1 yr	Survival Mean (mo)	Quality Good	Quality Poor	Operative deaths	Complications (No. of patients)
Pneumonectomy	29	7 (6 alive)	7.4	9	20	5 (17%)	Empyema (1) Fistula (1)
Bronchial sleeve resection	18	9 (7 alive)	11.3	13	5	1 (5.5%)	Stenosis (2)

sible results at the smallest cost in function and mortality and with the best possible quality of survival for the patient.

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Treatment of Bronchogenic Carcinoma With Surgery and Radiotherapy: The Experience of the National Cancer Institute of Milan

Pietro Bucalossi, Gianni Ravasi, Federico Bozzetti, and Franco Milani [1,2]

SUMMARY

A series of 129 patients who received radical surgical treatment of lung cancer is reported. The patients were hospitalized between 1962 and 1971 at the National Cancer Institute of Milan, Italy, and were classified according to symptomatic and anatomic criteria. The survival rate was obtained by the actuarial method. The results of therapy were considerably better in those patients who had only pulmonary symptoms or patients who were asymptomatic without localized regional disease spread. The results achieved in 276 patients with inoperable lung carcinoma are also reported. Radiotherapy was administered to these patients with cobalt 60 units. It may be possible to improve the prognosis by combining surgical treatment, radiotherapy, chemotherapy, and immunotherapy through appropriate clinical trials.
[Cancer Chemother Rep Part 3, vol 4:101–107, 1973]

The surgical treatment of lung cancer at the National Cancer Institute of Milan was started around 1950. At first, the number of patients was limited and in the majority of cases, the disease was already in an advanced stage. During those early years, most of the patients that were hospitalized were treated with radiation, and most of the thoracotomies performed were of a purely exploratory nature. Later on, the technical advances in both surgery and anesthesia which had been made in the Institute and the increased number of beds led to a greater number of admissions and to an expansion of surgical therapy. For this reason, we have chosen the last 10 years as the period for this survey.

[1] National Cancer Institute, Milan, Italy.
[2] *Reprint requests to:* Dr. Gianni Ravasi, via Venezian 1, Milan 20133, Italy.

SURGICAL TREATMENT

Patients

Of 526 patients with bronchogenic carcinoma treated at the National Cancer Institute of Milan between 1962 and 1971, 348 were determined to be inoperable when admitted without exploration. In 37 patients of the 178 who received thoracotomy, the operation was solely exploratory. Of the remaining 141 patients, we shall deal only with the 129 who survived the operation. (The apparently high mortality rate of 10% is explained by very high figures during the first 5 years; the rate is now less than 3%.) In table 1 we have divided, year by year, the number of operations carried out. During the more recent years, a notable increase in surgical therapy can be seen.

TABLE 1.—Number of patients entered into surgical treatment program from 1962 to 1971

Mode of surgical treatment	Year of entry										Total
	62	63	64	65	66	67	68	69	70	71	
Lobectomy	2	1	3	4	3	2	11	18	16	11	71
Pneumonectomy	4	3	3	2	8	2	11	11	8	6	58
Total	6	4	6	6	11	4	22	29	24	17	129

Extent of Disease

For an appraisal of the results of surgical therapy, we have classified our patients according to two criteria: (*a*) anatomic site and regional extension (table 2), and (*b*) symptomatic stage, similar to that proposed by Feinstein (1) (table 3). Actually, in our staging we have not made a distinction between long-lived pulmonary disease and short-lived pulmonary disease (stage II, A and B), because of the difficulty of pin-pointing the chronologic evolution of the disease in a mainly retrospective study, and because of the high incidence of comorbidity, which makes the interpretation of the symptoms very difficult. Furthermore, pulmonary symptoms are, for the most part, dependent upon the site of the origin of the tumor, and determining the origin of the tumor necessitates the subdivision of each stage into central and peripheral tumors, thereby incurring the risk of having such small numbers that they are statistically meaningless.

In order to evaluate the results, we have combined in the second stage patients with pulmonary symptoms of more and less than 6 months' duration. In table 4, patients are classified according to symptomatic stages. Note that there are a large number of patients in the second stage, whereas there are none in the fourth and fifth stages (which do not enter into any consideration of surgical therapy).

In table 5, patients are subdivided according to site and anatomic stage. It can be seen that central tumors metastasize more readily (17 of 61) than peripheral tumors (ten of 68) and are also less readily extended (eight of 61 versus 12 of 68). If the anatomic stage is considered in relation to the histologic type (table 6) it can be seen that the tendency to metastasize to the nodes is slightly greater for adenocarcinomas (30% of the central tumors and 11% of the peripheral tumors). While squamous cell carcinomas are equally divided between central and peripheral sites, adenocarcinomas are more frequently peripheral. Peripheral adenocarcinomas extend more readily than the corresponding squamous cell forms.

TABLE 2.—Anatomic staging adopted for operable bronchogenic carcinoma at the National Cancer Institute of Milan

Site	Stage*
Central tumor (C):	L
localized to the main or lobe bronchus	E
	N
	EN
Peripheral tumor (P):	L
localized to segmental or subsegmental bronchi	E
	N
	EN

*L = localized to the bronchus and surrounding pulmonary tissue; E = extended to adjacent tissues (eg, pleura, pericardium); N = nodal involvement of hilus and mediastinum; EN = extended and with nodal involvement.

TABLE 3.—Symptomatic staging adopted for operable bronchogenic carcinoma at the National Cancer Institute of Milan

Stage	Description
I	Asymptomatic
II	Pulmonary symptoms (*A*) ≥6 months' duration (*B*) <6 months' duration
III	Stage II plus systemic symptoms
IV	Symptoms of mediastinal involvement
V	Symptoms due to distant metastases

TABLE 4.—Number of patients surgically treated for bronchogenic carcinoma in relation to symptomatic stage

Stage	No. of patients treated
I	19
II	
A	42
B	51
III	17
IV	—
V	—

TABLE 5.—Number of patients surgically treated in relation to initial site and anatomic stage

Site	No. of patients treated	Anatomic stage*			
		L	E	N	EN
Central	61	33	8	17	3
Peripheral	68	42	12	10	4
Total	129	75	20	27	7

*See footnote, table 2.

TABLE 6.—Cell type in relation to initial site and anatomic stage

Cell type	Site	Anatomic stage*				Total No. of patients treated
		L	E	N	EN	
Epidermoid carcinoma†	C	26	8	12	2	48
	P	25	6	4	2	37
Adenocarcinoma	C	3	0	2	0	5
	P	13	5	4	2	24
Undifferentiated large cell carcinoma	C	1	0	3	0	4
	P	3	1	1	0	5
Undifferentiated small cell carcinoma	C	3	0	0	1	4
	P	1	1	0	0	2
Total		75	21	26	7	129

*See footnote, table 2.
†C = central; P = peripheral.

Results

In order to evaluate the results, we have determined survival curves according to the actuarial method in relation to the histologic type (fig 1) and the anatomic (fig 2) and symptomatic (fig 3) stages. We were surprised to discover that the results we obtained are somewhat different from those reported by other investigators (2). However, the two curves representing the undifferentiated forms of carcinoma (large and small cell) show such a small number of patients that the presence of one or more long-term survivors could change the whole aspect of the curve. Furthermore, we have obtained median value figures which are practically identical for squamous cell tumors and adenocarcinomas. This peculiar result can be explained in part by the fact that the stage of localized regional extension (stage N, E, or NE) of the two types of cancer was practically the same (40% of the cases).

The importance of localized regional spread to prognosis is clearly shown in figure 2, in which the survival curves are shown in relation to the anatomic stage. From this it appears that the most responsive component, of all cases considered, is the peripheral localized form (PL), which has a 50% response rate.

Survival figures in relation to the symptomatic stage shown in figure 3 reveal how little importance subjective symptoms have in the prognosis. In fact, apart from the systemic symptoms curve, which seems to show clearly the deterioration in stage III, there does not seem to be any difference between asymptomatic patients (stage I) and those with pulmonary symptoms (stage II). In effect, there are patients in the asymptomatic stage in whom the diagnosis is not necessarily initial but simply random, and who have tumors in different stages of evolution and with varying degrees of malignancy.

RADIOTHERAPY

The experience achieved in the Department of Radiology of the National Cancer Institute of Milan is briefly summarized here.

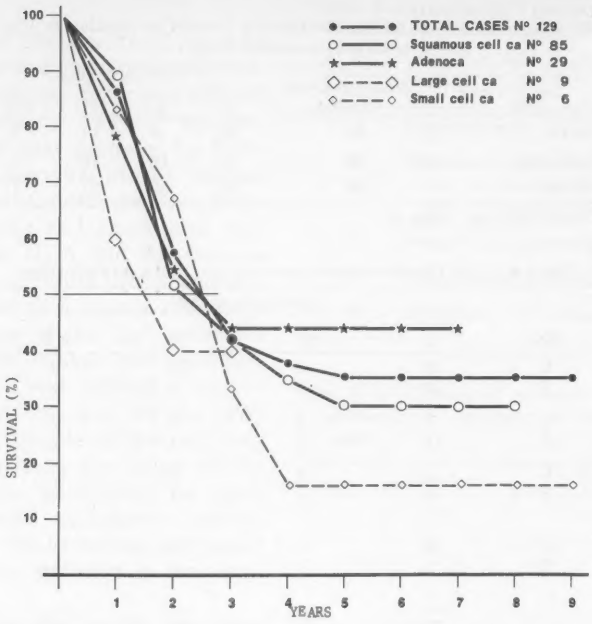

FIGURE 1.—Survival time in relation to histologic type of cancer.

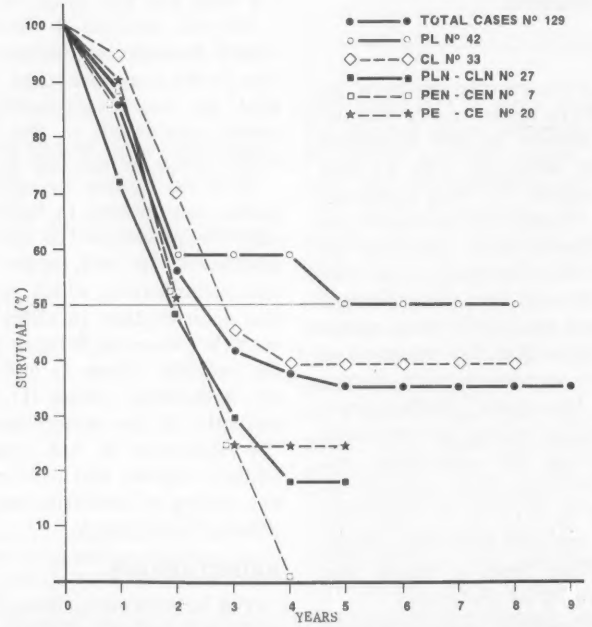

FIGURE 2.—Survival time in relation to anatomic stage of disease (*see* table 2 for definitions of anatomic stages).

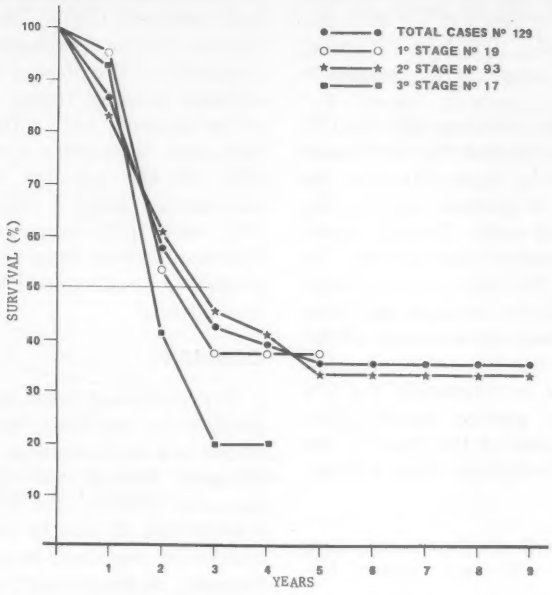

FIGURE 3.—Survival time in relation to symptomatic stage (1° = stage I, 2° = stage II, 3° = stage III; *see* table 3).

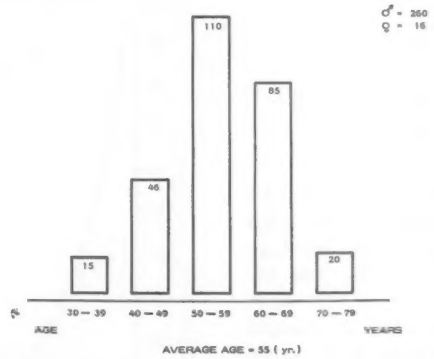

FIGURE 4.—Age distribution of patients treated with telecobalt therapy from June 1958 to June 1965 (276 patients).

Patients and Methods

Patients were referred to the Department of Radiology either from the clinical wards of the Institute or directly from the Outpatient Department. The observations cover a period from 1958 to 1965 and include a total of 276 cases of inoperable pulmonary carcinoma.

In figure 4, the distribution of the patients is shown according to age. The major incidence of the disease was in patients between 50 and

70 years of age. In 243 patients (88%) the tumor had a central site (eg, mediastinum plus hilus), and in only 33 cases (12%) was the tumor located peripherally. Of these 33 cases, 18 (6.6%) had apical origin with Pancoast's syndrome.

Diagnoses were made histologically in 152 patients (55%). In particular, in 101 cases (66%) the diagnosis was made through the cytologic examination of sputum, and in the other 51 (44%) it was made through endoscopic biopsy or explorative thoracotomy. In the remaining patients, the diagnosis was made using radiologic and clinical findings, and was later confirmed by the progressive nature of the disease. From the histologic point of view, since it is frequently difficult or impossible for the pathologist to reach a precise classification from cytologic examination of the sputum, we have subdivided the patients into three groups, as shown in table 7.

TABLE 7.—Patients treated with telecobalt therapy from June 1958 to June 1965 (152 cases diagnosed histologically).

Histologic type	No. of patients	Percent
Differentiated carcinoma (squamous cell and adenocarcinoma)	66	44
Undifferentiated carcinoma (oat cell and large cell)	52	34
Undetermined carcinoma	34	22
Total	152	

Radiotherapy was administered with cobalt 60 units. The fixed-field technique was used in most patients (217 cases). The moving-field technique was restricted to the less extended central forms (59 cases). The dose delivered to the majority of patients ranged between 4000 and 6000 rads over 40–50 days, depending upon the extension of the tumor, the localized regional condition, and the aim of the therapy.

Results

The results of radiotherapy are shown in terms of survival (fig 5). The curve shows that 1 year after radiotherapy 98 patients had survived (36%), after 2 years 36 patients had survived (13%), and after 3 years 19 patients had survived (7%). The survival curves in relation to the histologic type show that the prognosis of the disease is better in the differentiated types of tumor (fig 6). In fact, 41% of the patients with differentiated carcinomas were still alive after 1 year in comparison to 21% of the patients with undifferentiated carcinomas. After 2 years these values fell to 15% and 10% respectively. With time, the distance between these two curves becomes progressively smaller until they become practically identical.

COMMENT

Every attempt must be made to control and possibly to eradicate small occult metastases which can be present at the time of surgery. Surgical therapy and radiotherapy have apparently come to the end of their individual possibilities. It may be possible to improve our results by combined surgical treatment, radiotherapy, chemotherapy, and possibly immunotherapy through appropriately controlled clinical trials.

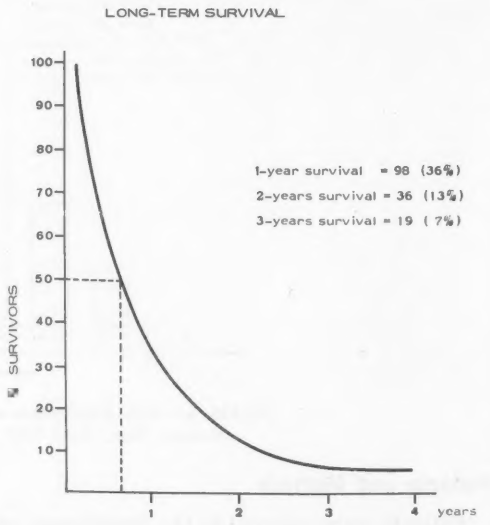

FIGURE 5.—Long-term survival curve for patients treated with telecobalt therapy from June 1958 to June 1965 (276 patients).

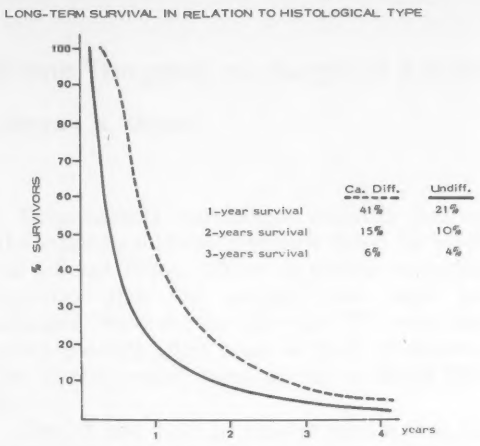

FIGURE 6.—Long-term survival in relation to histologic type for patients treated with telecobalt therapy from June 1958 to June 1965 (276 patients).

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Some Thoughts on Surgical Adjuvant Studies in Lung Cancer

Stephen K. Carter [1]

Bronchogenic carcinoma presents one of the more formidable problems faced by medical science today. There is strong statistical evidence that the overall cure rate has changed little during the past 30 years and every possible effort must be made to improve the dismal overall survival rate of about 7%–8%.

One of the most promising approaches has been surgical adjuvant chemotherapy in patients undergoing resection for the disease. To date, this therapy has not been successful but few drugs have been evaluated and the study designs have been variable. It is the purpose of this paper to review some of the problems encountered in surgical adjuvant studies and make some recommendations for the design of future investigations.

Surgical adjuvant studies, like all clinical trials, must be designed with consideration of three broad parameters:

1. Patient selection—the status of the patient before therapy,
2. Therapy, and
3. Evaluation of response—the status of the patient after therapy. In planning a surgical adjuvant study for bronchogenic carcinoma, each of these areas must be given equal importance despite the fact that attention is generally devoted predominantly to therapy.

PATIENT SELECTION

Patients with an initial diagnosis of bronchogenic carcinoma fall into one of two groups—operable or inoperable. Naturally, the operable group is concerned in surgical adjuvant chemotherapy, and the critical question is whether or not "operability" is consistently defined among the various groups performing the studies. Unfortunately, the published literature and protocols on file in the Cancer Therapy Evaluation Branch (CTEB) do not answer this question, but they do show that different investigations have used various mixes of five therapy groups for operable patients:

1. Curative resection with patients classified by various parameters as "good risk" for cure.
2. Curative resection with patients classified by various parameters as "poor risk" for cure.
3. Palliative resection even though tumor is not removed.
4. Patients found inoperable after thoracotomy and no resection is performed.
5. Patients refusing surgery.

A highly desirable feature in the design of future studies would be to define, as completely as possible, the median time to recurrent disease for each therapy group, as well as the survival curve. This would allow a decision on whether adjuvant therapy should be attempted in each group and would gauge the value of stratification if more than one group is involved.

Figure 1 outlines a general flow of therapy for patients with bronchogenic carcinoma. Each patient category could possibly be assigned an individual protocol geared specifically to the risk factors involved, with a further breakdown by histologic cell type.

A review of past and present studies reveals that patient selection groups have not been comparable. This is illustrated by the four selected studies in table 1; none of the four employ an identical population. The protocol of the Veterans' Administration Surgical Adjuvant Group is restricted essentially to what might be termed curative resection but "poor risk" for cure. All patients with undifferentiated lesions (either large or small cell) are included,

[1] Cancer Therapy Evaluation Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

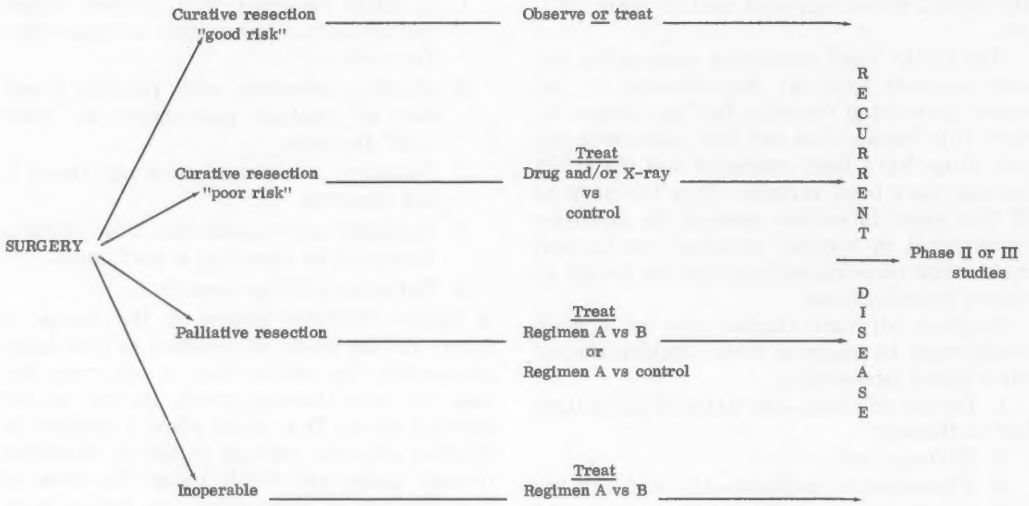

FIGURE 1.—General flow of therapy for patients with bronchogenic carcinoma.

while only squamous cell or adenocarcinoma patients with selected "poor risk" factors are studied. The University Surgical Adjuvant Lung Project (1) included curative "good risk," curative "poor risk," and palliative categories with stratification in each group. The Swiss Chemotherapy Group (2) used only a curative resection category and did not define a good or poor risk group. A recently proposed study of the Mayo Clinic is restricted to patients who have had curative resections with some degree of "poor risk" and excludes differentiated squamous cell carcinoma patients without lymph node metastases as well as grade I and II adenocarcinoma patients.

Table 2 compares the number of patients registered or screened with the number actually entered in the three most recently reported studies. In each study, over 60% of the patients were excluded. The results, or lack thereof, in these highly selective populations may not be applicable to over one half the patients

TABLE 1.—Comparison of patient selection factors among various surgical adjuvant lung study groups

Study group and protocol	Patient selection factors
VA Surgical Adjuvant Group, Protocol No. 21 Control vs cyclophosphamide + methotrexate vs cyclophosphamide alone	1. Male patients 2. No previous operation for malignant lesion 3. No prior irradiation during the previous 6 mos 4. No previous surgery for a second primary tumor 5. Primary lesions removed with no microscopic evidence of residual disease but resected specimen shows any of the following: *a.* Undifferentiated carcinoma or small or large cell carcinoma *b.* Blood vessel invasion *c.* Lymphatic invasion *d.* Invasion of visceral pleura *e.* Positive lymph nodes *f.* Tumor in other organs or tissue removed *g.* Final pathologic classification—neoplasm extending beyond the lung
University Surgical Adjuvant Lung Project Control vs mechlorethamine	Exclusions: 1. Current cancer treated during the previous 6 months 2. Previous or concomitant cancer 3. Nonresectable disease 4. Pulmonary tumors other than carcinoma 5. Active tuberculosis Treated patients are grouped and stratified as follows: *a.* Category 1: lesion limited to the lung and no positive lymph nodes found *b.* Category 2: lesion confined to the lung and hilar or mediastinal lymph nodes and all involved tissue resected *c.* Category 3: extensive tumor involvement: resection was completed but surgeon recognized that tumor remained

TABLE 1.—Comparison of patient selection factors among various surgical adjuvant lung study groups—Continued

Study group and protocol	Patient selection factors
Swiss Chemotherapy Group	Exclusions:
Control vs cyclophosphamide	1. Clinically judged inoperable
	2. Palliative resection performed; only patients "radically resectable" included:
	a. Lobectomy 44.1%
	b. Pneumonectomy 40.8%
	c. Bilobectomy 11.2%
	d. Segmental resection 3.9%
Mayo Clinic (proposed study)	"Curative" resection with the following exclusions:
	1. Any other disease that would seriously affect prognosis or contraindicate intensive chemotherapy
	2. Inability to return to Mayo Clinic for appropriate followup examination
	3. Well-differentiated squamous cell carcinoma without lymph node metastases
	4. Grade I and grade II adenocarcinoma

initially diagnosed as having bronchogenic carcinoma. This fact is not cited in a critical vein but rather to suggest that protocols specifically designed for all of the therapeutic categories might provide more critically needed information by making use of the entire patient population initially available for study.

Other factors influence the prognosis of patients with bronchogenic carcinoma who undergo resection, and these factors should be seriously considered for stratification in future studies. Cell type is the most obvious and repeatedly demonstrated factor. In the University Surgical Adjuvant Study, survival was poorest for the anaplastic cell type and relatively good for the bronchiolar type. Adenocarcinoma and squamous cell types were somewhat similar and intermediate in survival between the other two types. The Swiss Chemotherapy Group has reported a higher recurrence rate for anaplastic and oat cell lesions than for epidermoid and adenocarcinoma le-

TABLE 2.—Patients registered or screened compared with patients entered on study in lung surgical adjuvant studies

Group	No. of patients registered or screened	No. of patients entered	Percent excluded
University Surgical Adjuvant Lung Project	3758	1222	67
Swiss Chemotherapy Group	504	189	62
VA Surgical Adjuvant Group, Protocol No. 21	2686	290	89

sions. Among 685 patients undergoing resections for cure from 1950 to 1957 at the Mayo Clinic, the 5-year survival rates by cell type were: squamous cell carcinoma, 36.5%; adenocarcinoma, 33.8%; large cell carcinoma, 28.7%; and small cell carcinoma, 10.3%. In all probability, stratification by cell type should be included in the design of future studies.

Another significant prognostic determinant is tumor size. The University Surgical Adjuvant Study noted a marked reduction in 5-year survival as tumor size increased, with better than 30% survival for the smallest tumors (<2.0 cm diameter) versus approximately 10% survival for the largest tumors. Steele et al (3) found that 308 patients having "curative" resections of lesions as large as 6 cm in diameter had a 5-year survival rate of 38.6%. In a select group of patients with lesions of 2 cm or less, the 5-year survival rate was 53%. Obviously, tumor size is another variable that should be seriously considered for stratification.

In summary, the planning of surgical adjuvant studies in bronchogenic carcinoma must include careful consideration of many factors that can significantly affect both prognosis and survival. These should be handled by stratification before randomization so that optimal homogeneity is obtained in control and treatment groups. For example, the patient selection factors outlined in figure 2 would yield 32 groups for analysis before randomization in a single protocol. On the other hand, with a separate protocol for each of the four categories of therapy there would be eight groups for randomization in each case. This number might be reduced through a mechanism incorporating tumor size into the separation of "good" and "poor" risks for curative resection.

THERAPY

At this time, none of the surgical adjuvant studies in lung cancer have shown any benefit for chemotherapy, and one study employing cyclophosphamide apparently had negative effects (2).[2] All of the studies have used the classic alkylating agents, mechlorethamine and cyclophosphamide. The only exception is the current VA Surgical Adjuvant Group protocol in which one treatment arm is cyclophosphamide and methotrexate in alternating monthly courses of 5 days of therapy.

The early studies were conducted on the premise that chemotherapy would destroy tu-

[2] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

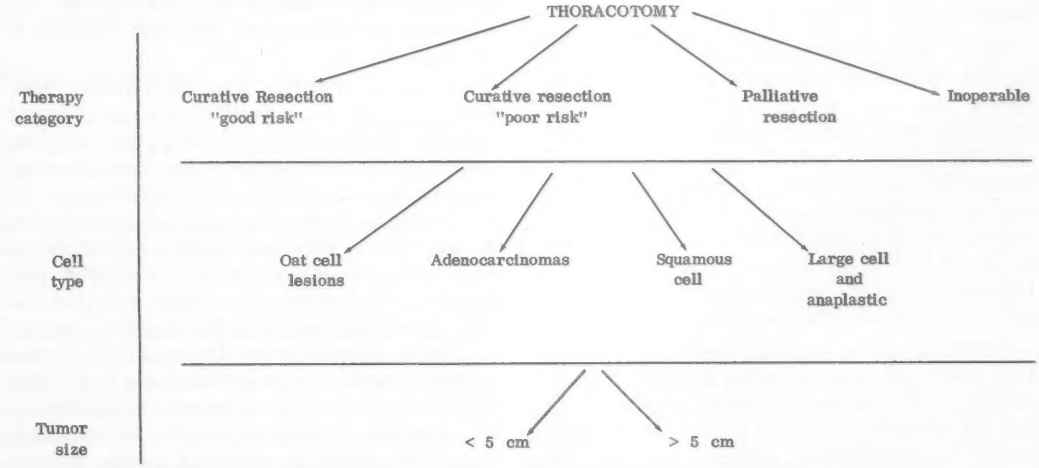

FIGURE 2.—Outline of potential pretherapy stratifications for lung surgical adjuvant studies.

mor cells released into the wound and circulation at the time of surgery. However, there is no direct evidence that a "shower of cells" at the time of surgery is a dominant cause of metastases. As pointed out by Slack (1) and others, the early recurrences after surgery, evidenced by initial sharp drops in survival curves, suggest that tumor cells are disseminated before surgery. It is unlikely that circulating tumor cells, or even clumps of cells, could lodge and proliferate into a tumor of clinically detectable size within a few months after surgery.

It is now generally accepted that successful chemotherapy in the adjuvant situation requires long-term administration. This is supported by the data of Steele and Lamerton (4) showing that the estimated median doubling time of primary lung carcinoma is 62 days, with a range of 17–200 days. If this is also true for metastatic deposits, it is highly unlikely that one or two "courses" of chemotherapy could destroy enough tumor cells to markedly affect survival.

Thus, the critical questions about therapy include the choice of drugs and schedules of administration, the time of initiation of therapy and its duration, and the level of drug toxicity to be sought in the host.

Drugs

There seems little to be gained by continuing the practice of evaluating single alkylating agents. One could argue that the durations of treatment with mechlorethamine (5–11) have not been long enough to produce significant results or that the optimal schedule and intensity of cyclophosphamide (12, 13) are unknown, but it is still difficult to be enthusiastic about additional studies with these drugs. Instead, there are several single agents that offer considerable promise at this time.

CCNU is active against metastatic disease (14) and may produce some survival gain in patients with "extensive disease" as defined by the VA Surgical Adjuvant Group. It is highly active in experimental systems and has the advantage of not being a "classic" alkylating agent. The drug is extremely simple to administer (15), with a single oral dose given every 6–8 weeks being probably as close as possible to an optimal schedule.

Hydroxyurea is reported to have activity against metastatic disease (16). In one study of the VA Surgical Adjuvant Group, hydroxyurea showed statistically significant superiority over placebo for prolonging the survival of patients with "extensive disease." It has the advantage of being a pure S-phase-specific drug. It is cell cycle-specific in L1210 leukemia, without self-limitation, and on its optimal schedule it can produce a "cure" in this system (17). Using the data obtained in experimental systems, one can postulate that microscopic metastatic foci grow in a Gompertzian manner, ie, initially the growth fraction is high and the doubling time rapid. If this is so, a pure S-phase-dependent drug like hydroxyurea might be more active than an alkylating agent. In addition, hydroxyurea has the crucially important advantage of being available in an oral formulation. This means that continuous blood levels can be maintained for as long as necessary through dose schedules that are not technically unfeasible in a surgical adjuvant situation. It should not be difficult to devise an oral dose to be given every 8 hours for 30–45 doses monthly over an extended period to maintain a continuous blood level for 10–15 days at a time. If this level is high enough, the cell kill could be higher than has been reached in the past.

The use of multiple drug combination regimens may also be a fruitful avenue of investigation. Extraordinary activity has been reported for the nitrosoureas plus cyclophosphamide in experimental tumors investigated by the Southern Research Institute. Specifically, the activity of this combination in the Lewis lung carcinoma-surgical adjuvant model is particularly interesting. The only disadvantage with cyclophosphamide is the negative data of the Swiss Chemotherapy Group showing that intensive weekly usage of this drug had harmful effects on survival compared with controls (2). Another problem is that the experimental data was generally obtained using methyl-CCNU. This drug is still in the early stages of clinical trial and the combination of methyl-

CCNU and cyclophosphamide is only now being fully evaluated in phase II study.

CCNU and hydroxyurea is another combination with possible efficacy because of the reasons given earlier for their use as single agents. Together, they would combine the activities of a cell cycle-insensitive agent (CCNU) and a cell cycle-sensitive agent (hydroxyurea). The sequential schedule developed by Hansen et al (19) could then provide a test of Schabel's elegant hypothesis (18) for using tumor growth kinetics in planning "curative" chemotherapy of advanced solid tumors at an earlier stage of disease.

Schedules of Administration

Based on the data obtained in experimental systems and clinical studies, the following schedules could be recommended.

1. CCNU: single oral dose every 6–8 weeks.
2. Hydroxyurea: daily divided dose (every 8 hours).
3. Nitrosourea + cyclophosphamide: CCNU or methyl-CCNU (single oral dose every 6–8 weeks) + cyclophosphamide (every 3 weeks).
4. CCNU + hydroxyurea: CCNU (single oral dose every 6–8 weeks) + hydroxyurea (daily or twice weekly in divided doses every 8 hours).

Initiation of Therapy

The original studies, including those of the University Surgical Adjuvant Group, started therapy on the day of surgery. Although the data are not totally conclusive, it does appear that complication rates were increased by initiating therapy at this time. The Swiss Chemotherapy Group began therapy with cyclophosphamide 7–14 days after surgery, and the VA Surgical Adjuvant Group currently begins chemotherapy between 14 and 30 days after surgery. It is possible that within 30 days after surgery one doubling of a metastatic focus could occur. This risk versus the possibility of increased postoperative complications is a problem the medical oncologists and surgeons must consider and resolve together.

Duration of Therapy

There is no evidence to support treatment for less than the 18 months currently utilized by the VA Surgical Adjuvant Group.

Level of Toxicity

A recent report of a current Surgical Adjuvant Study Group protocol on file with the CTEB notes that hematologic toxicity was seen in only 11%–22% of 952 courses of drug administered. This raises a critical question—if no toxicity develops in a patient after drug administration, can that patient be considered evaluable for drug effect? Or, phrased another way, should protocols be designed to include dose escalation to obtain a slight degree of hematologic toxicity? Inclusion of this element in protocol design would insure that biologically active blood levels of drug are attained in all patients.

EVALUATION OF RESPONSE

Survival is a clear-cut and easily determined parameter that has been the traditional end-point of surgical adjuvant studies. However, it does have disadvantages.

A survival end-point can and does make the duration of study extremely long. While 5-year survival may be the ultimate point of evaluation, it would be highly desirable to make rapid assessments that, at least, would allow suspension of studies having poor prospects for useful results.

When survival is the sole measure of effectiveness, patients may not be given additional therapy at the time of recurrent disease. If they are, there is the risk that it will affect survival and cloud the results of the study. It would be most helpful, for the patients as well as the acquisition of data, if they could be entered on additional studies at the time of recurrent disease.

Time to recurrent disease or length of disease-free interval might be more useful end-points. In his detailed report of the University Surgical Adjuvant Group, Slack (1) pointed out that examination of recurrence rates and/or disease-free interval led to much the same conclusions as those reached on the basis of

survival. Recurrence rates were similar to death rates or the compliment of survival rates. The use of disease-free interval would make patients available for phase II or III studies and would allow maximum use of the available patient population. In addition, it would avoid the ethical problem of denying possibly beneficial therapy to patients because of study design considerations.

Perhaps the greatest need in surgical adjuvant studies is for designs that furnish rapid answers so that more studies can be performed and more questions answered. Massive data with clear survival and recurrence curves are available for post-surgery patients. These could be used in conjunction with results from concurrent controls to rapidly evaluate data in current studies. For example, the historical data could provide percent recurrence rates after surgery at fixed times (eg, 6, 9, and 12 months) in the treatment and control groups. With this data, it should be possible for statisticians to determine the probability of a given treatment ultimately being, for example, 50% better than control if at 6 months the recurrence rates are equal. In the event of a slim probability, the study could be suspended immediately and a new one initiated. Obviously, development of such studies will require considerable effort and coordination among clinical investigators and statisticians, but the need for rapidly increasing understanding in this crucial area certainly requires, at least, careful thought directed to new approaches.

CONCLUSIONS

A combination of therapeutic modalities used early in the course of disease probably offers the best chance for markedly improving the survival rate among patients with solid tumors. The use of chemotherapy immediately after surgery is highly attractive because of the potential of drugs for killing tumor cells that are inaccessible to surgical excision or ablation by radiotherapy. Thus far, however, studies combining drugs and surgery in the treatment of lung cancer have suffered from many shortcomings. Patient selection factors have been highly variable and only a small part of the bronchogenic carcinoma patients receiving thoracotomy have been effectively treated. The chemotherapy employed has been of ineffective duration and, probably, ineffective intensity. Finally, the studies have required large numbers of patients and long periods of observation for evaluation of results.

The solution of these problems should have the highest priority in future deliberations on surgical adjuvant therapy.

LIST OF COMPOUNDS

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1

Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Methyl-CCNU: NSC-95441; CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-

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Status Report of Adjuvant Cancer Chemotherapy Trials in the Treatment of Bronchial Carcinoma

T. W. Shields [1]

SUMMARY

A total of 2718 men with bronchial carcinoma have been included in prospective randomized clinical trials of adjuvant chemotherapy and resection versus resection alone. The drug regimens have utilized mechlorethamine, cyclophosphamide, and cyclophosphamide alternating with methotrexate. Neither a beneficial nor a harmful effect has been noted; the survival rates in both the treated and control groups have been essentially the same.

[Cancer Chemother Rep Part 3, vol 4:119–124, 1973]

During the past 15 years, the Veterans' Administration Surgical Adjuvant Cancer Chemotherapy Group [2] has conducted a series of prospective randomized clinical trials to evaluate the use of adjuvant chemotherapy after surgical resection of bronchial carcinoma. The selection of the patients has been relatively similar in each trial; the drugs used in the study have been mechlorethamine, cyclophosphamide, and methotrexate.[3] A total of 2718 patients have been admitted to either one of the treatment groups or to one of concurrently conducted control groups. In addition, 331 patients were randomized in a preoperative radiation therapy trial (1).

MATERIALS AND METHODS

All patients entering the trials had to be male patients undergoing resection of primary bronchial carcinoma. Specifically excluded from the studies were patients who had distant metastases; patients who had had a previous operation for the same malignant lesion of the lung; patients who had had a previous operation for or a diagnosis of a second primary cancer, except for cancer of the skin or

[1] Department of Surgery, Veterans' Administration Research Hospital, Chicago, Ill.

[2] VAH, Boston, Mass (Dr. Richard W. Dwight, secretary [Site Chairman, Colon]); VAH, Bronx, NY (Dr. E. Converse Pierce); VAH, Brooklyn, NY (Dr. Harry LeVeen); VAH, Chicago (Research), Ill (Dr. Thomas Shields [Site Chairman, Lung]); VAH, Cincinnati, Ohio (Dr. Carl G. Schowengerdt); VAH, Cleveland, Ohio (Dr. Jerry S. Wolkoff); VAH, Dallas, Tex (Dr. Robert P. Hays); VAH, East Orange, NJ (Dr. Oscar Serlin [Site Chairman, Stomach]); VAH, Hines, Ill (Dr. William S. Walsh); VAH, Houston, Tex (Dr. Paul H. Jordan, Jr.); VAH, Iowa City, Iowa (Dr. Richard L. Lawton); VAH, Jackson, Miss (Dr. J. Harold Conn); VAH, Kansas City, Mo (Dr. Alfred Heilbrunn); VAH, Long Beach, Calif (Dr. George L. Juler); VAH, Martinez, Calif (Dr. James Yee); VAH, Memphis (Kennedy), Tenn (Dr. Joseph McCaughn); VAH, Minneapolis, Minn (Dr. Edward W. Humphrey); VAH, Philadelphia, Pa (Dr. Stanley J. Dudrick); VAH, Pittsburgh (University Dr), Pa (Dr. Dan Elliott); VAH, Providence, RI (Dr. Harold W. Harrower); VAH, San Juan, Puerto Rico (Dr. Jose H. Amadeo); VAH, St. Louis, Mo (Dr. Robert C. Donaldson); VAH, Syracuse, NY (Dr. Lloyd Rogers); VAH, Wood, Wis (Dr. Gale L. Mendeloff); VAH, Washington, DC (Dr. George A. Higgins, Jr. (chairman); VACO, Washington, DC (Dr. Lyndon E. Lee, Jr.); NAS-NRC, Washington, DC (Mr. Seymour Jablon (statistician).

[3] Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard.

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan.

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

lip; patients who had had treatment during the previous 6 months with radiation (except to skin or lip) or chemotherapy; patients who had active pulmonary tuberculosis; patients who had consistently depressed leukocyte or platelet counts; and patients who had a diagnosis of bronchial adenoma.

The resection was classified as either curative or palliative; the latter classification was applied only if tumor was demonstrated at the line of resection or if residual tumor, proved by biopsy, was left in the thorax at the completion of the procedure. Pathologically, the tumors were grouped into one of three categories: squamous cell, adenocarcinoma, or undifferentiated cell types.

In each trial, the patients were randomly assigned to a treatment or control group by the British envelope system. In the initial trial, mechlorethamine was administered at a dose level of 0.4 mg/kg of body weight up to a maximum of 30 mg, with 0.2 mg/kg given on Day 0 and 0.1 mg/kg/day given for 2 subsequent days. On Day 0, the dose was divided and half was given intrapleurally at the completion of operation and the other half was given intravenously (iv). For the next 2 days the drug was given iv. In the second trial, the dose level of mechlorethamine was reduced to 0.3 mg/kg of body weight with a maximum dose of 22.5 mg, the initial iv dose being eliminated. During the interval between this and the next trial, two control groups coded as "Series X" and "compound 62–63" were studied.

A cyclophosphamide trial was then initiated for those patients in whom the diagnosis of bronchial carcinoma was not established until the time of thoracotomy. The drug was administered at a dose level of 6 mg/kg of body weight into the pleural cavity at the completion of the operation. The same dose was then given iv daily for the first 4 postoperative days; a second course of 8 mg/kg on 5 successive days was given in the fifth postoperative week.

After completion of this trial, a regimen of prolonged intermittent courses of either cyclophosphamide or cyclophosphamide alternating with methotrexate was begun and is still under study. A specific criterion established for selection of the patients for this trial was the presence of one or more unfavorable characteristics determined by the study of the resected specimen. These characteristics were undifferentiated carcinoma (small or large cell), blood vessel invasion, lymphatic invasion, involvement of the visceral pleura, lymph node invasion, tumor found in other organs or tissues removed, or a final pathologic classification of neoplasm extending beyond the lung. The patient was not randomized until the 14th postoperative day and was placed in either of the two treatment groups or the control group. Regimen A consisted of cyclophosphamide, 8 mg/kg of body weight given iv in five doses on consecutive days; the course was repeated every 5 weeks. Regimen B consisted of cyclophosphamide, 8 mg/kg of body weight administered iv on 5 consecutive days alternating at 5-week intervals with methotrexate administered iv or intramuscularly, 10 mg daily for 5 days. Both regimens A and B were to be continued for 18 months.

The number of control and treated patients entered into each trial is given in table 1. The number of patients receiving followup studies is shown by year from the date of randomization in table 2.

RESULTS

The 5- and 10-year survival rates of the treated and control patients in all the adjuvant chemotherapeutic trials as computed by the life-table method are essentially the same (fig 1) and no drug effect is noted. The 5-year survival rates are 21.4% and 23.3%, and the

TABLE 1.—Chemotherapy trials in lung cancer patients

Trial	No. of patients
Mechlorethamine, full dose	186
Mechlorethamine, reduced dose	956
Series X	24
Compound 62-63	114
Cyclophosphamide	1129
Cyclophosphamide, prolonged intermittent therapy	2718

TABLE 2.—Patients in followup study and percent survival by year from randomization

Year from randomization	Treated patients		Control patients	
	No. in followup study at start of year	Survival to end of year (%)	No. in followup study at start of year	Survival to end of year (%)
0–1	1398	51.7	1438	55.9
1–2	704	37.1	790	39.8
2–3	481	29.6	549	31.6
3–4	369	24.7	427	27.0
4–5	296	21.4	357	23.3
5–6	244	19.5	296	20.5
6–7	201	16.9	235	18.4
7–8	157	14.8	193	16.6
8–9	119	12.9	154	16.0
9–10	90	11.8	128	14.7
10–11	68	11.1	93	13.5
11–12	51	8.9	72	12.3
12–13	24	7.8	53	10.3
13–14	9	6.9	29	9.4

10-year survival rates are 11.8% and 14.7% respectively.[4]

In comparing the percentage of survivors receiving a curative resection and eliminating all those patients dying during the first 30 days postoperatively, no treatment effect, either beneficial or harmful, is evident in the full-dose mechlorethamine trial (fig 2), the reduced-dose mechlorethamine trial (fig 3), or the initial cyclophosphamide trial (fig 4). Similar findings are recorded for the survivors from randomization in the prolonged intermit-

[4] Includes 331 patients admitted to the preoperative radiation therapy trial.

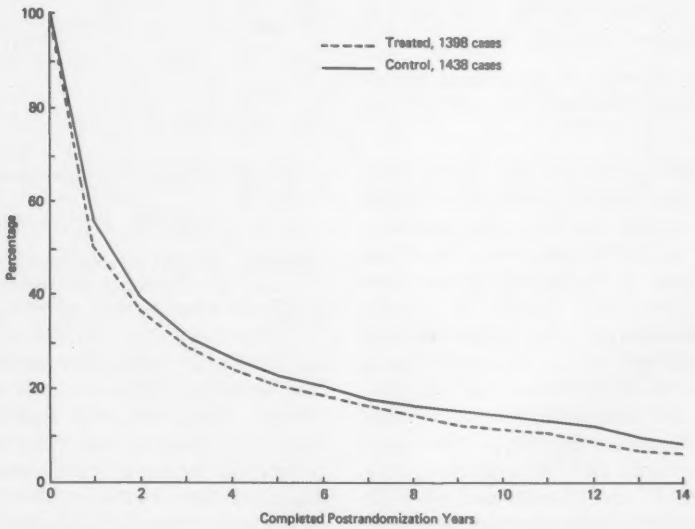

FIGURE 1.—Five- and 10-year survival curves for all patients admitted to the adjuvant chemotherapeutic trials.

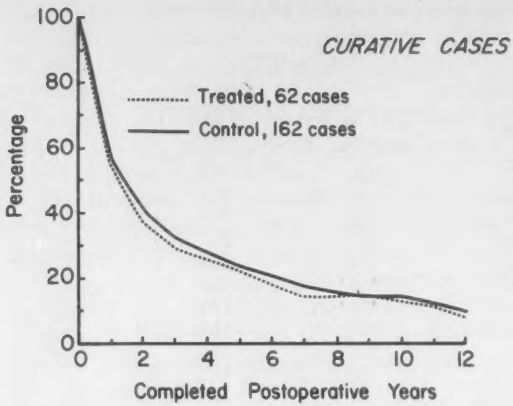

FIGURE 2.—Percent survival among patients treated with surgery and full-dose mechlorethamine: curative patients only.

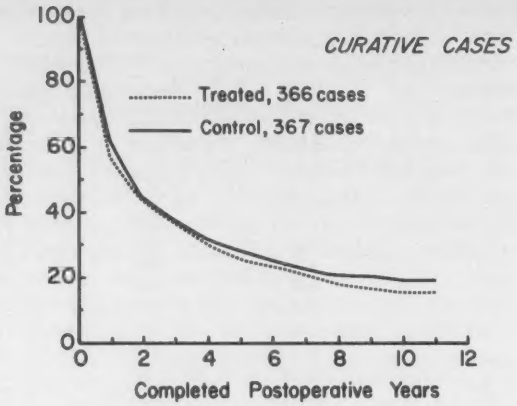

FIGURE 3.—Percent survival among patients treated with surgery and reduced-dose mechlorethamine: curative patients only.

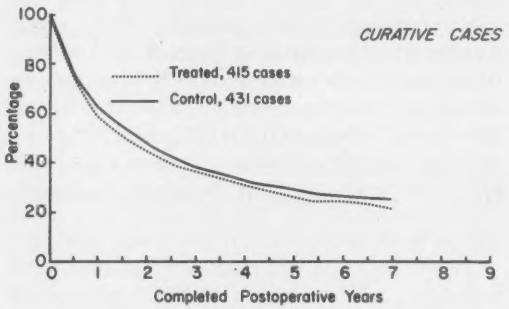

FIGURE 4.—Percent survival among patients treated with surgery and cyclophosphamide: curative patients only.

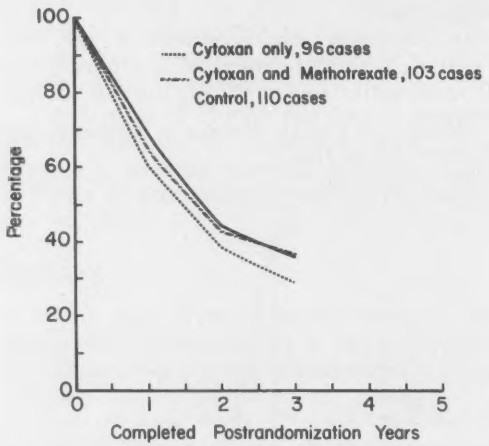

FIGURE 5.—Percent survival among randomized patients treated with prolonged intermittent therapy: all eligible patients.

tent therapy trial (fig 5). In this latter trial, the 3-year survival rates are 36.3% for the control group, 28.9% for the cyclophosphamide group, and 36.5% for the groups receiving alternating courses of cyclophosphamide and methotrexate.

With the accumulation of a great deal of data from the patients in the various trials, a number of features of the disease and its surgical treatment have become apparent. In combining the mechlorethamine trials (full- and reduced-dosage groups and the control groups including "Series X" and "Compound 62–63") it is readily apparent that younger patients do better than older ones (table 3), but again survival is virtually independent of treatment.

In the initial cyclophosphamide series there is also no drug effect, but when the group is broken down into cell types it is apparent that the results in oat cell tumors are much poorer, as measured by 5-year survival rates, than are the results in the other cell types which have essentially similar prognoses with respect to each other (table 4). Interestingly, however, as reported by Higgins (2), there is

TABLE 3.—Percent survival in completed lung trials

Mechlorethamine trial	No. of patients	Percent surviving through year— 5	10
Total			
Treated	536	22.6	12.7
Control	651	23.4	14.3
Age < 55 yrs			
Treated	125	32.8	24.8
Control	175	28.6	22.3
Age 55+ yrs			
Treated	411	19.5	9.0
Control	476	21.4	11.3

TABLE 4.—Percent survival in completed lung trials

Cyclophosphamide trial, curative patients	No. of patients	Percent surviving through year— 5	8
Total			
Treated	496	22.8	16.2
Control	512	25.2	18.9
Adenocarcinoma			
Treated	67	31.3	16.0
Control	86	22.4	19.0
Squamous cell			
Treated	251	26.5	20.8
Control	257	32.2	24.4
Oat cell			
Treated	32	9.4	—
Control	26	3.8	—
Other, mixed			
Treated	62	25.8	—
Control	61	27.9	—

a suggestion that cyclophosphamide may have some effectiveness when given as an adjuvant to the surgical procedure in the oat cell group, the 5-year survival rates being 9.4% in the treated patients and only 3.8% in the control patients. Unfortunately, the groups are too small to yield statistically significant results.

Higgins and Beebe (3), in evaluating the initial data from the trials, have pointed out that neither cell type (oat cell tumors being included in the undifferentiated cell group) nor tumor size was significant relative to prognosis in the patients undergoing resection. However, 13 other characteristics were found to influence 5-year cancer-free postoperative survival (table 5). In further evaluating the patient group, we (4) were able to determine four variables (disease limited to the lung, age of the patient, mediastinal lymph node involvement, and presence of other pulmonary disease) to which numerical values could be assigned, the sum of which gave a high level of association between the score and the prognosis of the patients. We found that the higher the score the greater the probability of recurrence of the disease (fig 6).

DISCUSSION

In men with bronchial cancer who have undergone a curative or palliative resection, the addition of various regimens of cancer chemo-

TABLE 5.—Relationship of 13 characteristics to 5-year cancer-free postoperative survival*

Characteristics	Effect of characteristic on cancer-free survival
Weight loss ≥ 10 lbs	Unfavorable
Age < 60 years	Favorable
Physical evidence of cancer	Unfavorable
Other pulmonary disease	Unfavorable
Operation on right side	Favorable
Pneumonectomy performed	Unfavorable
Obstruction of bronchus	Unfavorable
Blood vessel invasion	Unfavorable
Lymphatic invasion	Unfavorable
Lobar node involvement	Unfavorable
Hilar node involvement	Unfavorable
Mediastinal node involvement	Unfavorable
Tumor confined to the lung	Favorable

*Reproduced with permission from the *Journal of Thoracic and Cardiovascular Surgery* (ref 4).

therapy (mechlorethamine, cyclophosphamide, and methotrexate) has not altered the postoperative survival of the patients in any significant manner. In only one small subgroup (patients with an oat cell tumor diagnosis at the time of thoracotomy) was there any suggestion that the administration of cyclophosphamide was of any benefit. No harmful effect of the chemotherapy as suggested by the previously reported data of Brunner (5) could be discerned in our group by any of the evaluations which have been carried out.

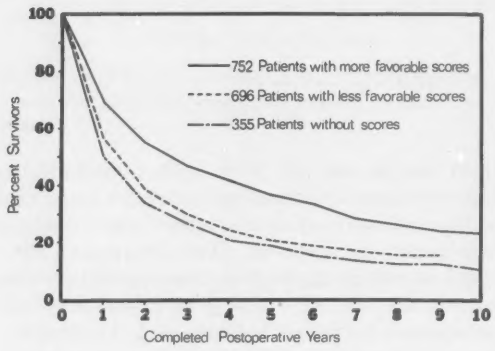

FIGURE 6.—Percent survival after curative surgery for bronchial carcinoma. Patients are grouped by magnitude of four-variable score predictive of outcome relative to mean score. [Reproduced with permission from the *Journal of Thoracic and Cardiovascular Surgery* (ref 4).]

The failure of the adjunctive chemotherapy utilized to date in increasing long-term survival is disappointing. However, a large volume of significant data concerning the disease has been accumulated and has made these studies valuable. Likewise, a well-tested clinical mechanism, the cooperative group, is available to evaluate any promising treatment regimens used in experimental and clinical studies of newer drugs now being carried out.

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Effects of Long-Term Adjuvant Chemotherapy With Cyclophosphamide (NSC-26271) for Radically Resected Bronchogenic Carcinoma [1]

Swiss Group for Clinical Cancer Research
Writing Committee: K. W. Brunner,[2] T. Marthaler,[3] and W. Müller [4]

SUMMARY

A controlled study of the effects of long-term adjuvant chemotherapy with cyclophosphamide during 2 years after radical resection of lung cancer is reported. A total of 172 patients (after exclusion of postoperative deaths and deaths from other causes during observation) were assigned at random to either no further treatment or treatment with cyclophosphamide. During an observation period of 3 1/2–5 1/2 years, 68% of the patients treated with cyclophosphamide had recurrences and 63% died, whereas, in the untreated control group, 49% of the patients had recurrences and 39% died. The disease recurred 8 months earlier in the treated group, and death occurred 8.8 months earlier. The different histologic types of lung cancer and operative procedures are described. The theoretical and practical implications of the study are discussed.

[Cancer Chemother Rep Part 3, vol 4:125–132, 1973]

From 1967 to 1969 the Swiss Group for Clinical Cancer Research, in cooperation with the Departments of Surgery of the five University Hospitals in Switzerland, studied the effects of long-term postoperative chemotherapy with cyclophosphamide in patients with lung cancer treated by radical resection.

PATIENTS AND METHODS

Patients were assigned at random to either no postoperative treatment (control group) or postoperative treatment with a total of six courses of intravenously (iv) administered cyclophosphamide over a period of 2 years. One course consisted of a total dose of 100 mg/kg of cyclophosphamide given in eight to nine weekly injections of 12 mg/kg. This left a mean period of 7 weeks of no therapy between the courses. The design of the study is outlined in table 1.

A total of 504 patients admitted by the Departments of Surgery for evaluation were considered for the study. One hundred and fifty-six patients had to be excluded according to protocol before operation because (*a*) their diseases were judged clinically inoperable (118 patients), (*b*) only palliative resection was planned (11 patients), or (*c*) no followup was possible (foreigners, etc; 27 patients). In 348 patients, radical resection was intended. Each of these patients was assigned a randomization card in a closed envelope which was to be

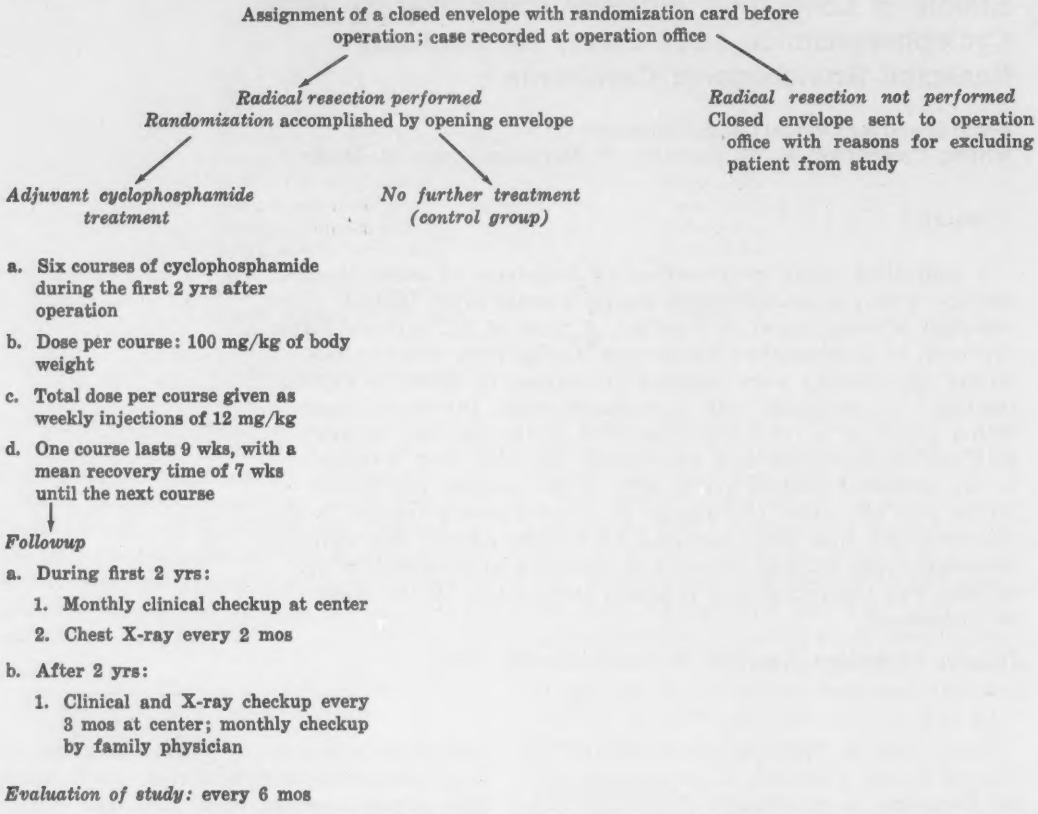
[1] Cyclophosphamide: CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan; Endoxan.

[2] Department of Clinical Oncology, Inselspital, Bern, Switzerland.

[3] Biostatistical Center, Faculty of Medicine, University of Zurich, Switzerland.

[4] Department of Surgery, Bürgerspital, Basel, Switzerland.

TABLE 1.—Cyclophosphamide adjuvant study: design of the study


Assignment of a closed envelope with randomization card before operation; case recorded at operation office
Radical resection performed
Randomization accomplished by opening envelope
Radical resection not performed
Closed envelope sent to operation office with reasons for excluding patient from study
Adjuvant cyclophosphamide treatment
No further treatment (control group)
a. Six courses of cyclophosphamide during the first 2 yrs after operation
b. Dose per course: 100 mg/kg of body weight
c. Total dose per course given as weekly injections of 12 mg/kg
d. One course lasts 9 wks, with a mean recovery time of 7 wks until the next course
Followup
a. During first 2 yrs:
1. Monthly clinical checkup at center
2. Chest X-ray every 2 mos
b. After 2 yrs:
1. Clinical and X-ray checkup every 3 mos at center; monthly checkup by family physician
Evaluation of study: every 6 mos

opened if radical resection was indeed possible. If this condition was not fulfilled, the closed envelope was sent to the operations office with detailed information on operative and histologic findings. This procedure was chosen to prevent selection of patients for the study after operation. On this basis, 159 patients had to be excluded after the operation according to protocol: for 87 patients, no radical procedure was possible; for 37 patients, a diagnosis other than bronchogenic carcinoma was made; 28 patients died during the first month after the operation; and seven patients were lost to followup after the operation. This left a total of 189 patients, who were randomized after radical resection was performed: 95 patients were assigned to the cyclophosphamide treatment group, and 94 were assigned to the control group.

Sixty-nine percent of the original 504 patients were operated upon. Forty-eight percent had radical resections. Twelve and one-half percent of those who had radical resections died during the first month after the operation.

RESULTS

The total number of recurrences and deaths from cancer after an observation period of 3½–5½ years is given in table 2. Patients in both groups who survived for 4 years had no further recurrences or deaths from cancer. All

TABLE 2.—Adjuvant cyclophosphamide study in patients with radically resected bronchogenic carcinoma

Group	No. of patients	No. of deaths from other causes	No. of evaluable cases	No. of recurrences (%)	No. of patients without recurrences (%)	No. of deaths from carcinoma (%)	No. of patients living with recurrences (%)
Adjuvant cyclophosphamide treatment	95	9	86	58 (68)	28 (32)	54 (63)	4 (5)
Control	94	8	86	42 (49)	44 (51)	34 (39)	8 (9)

patients who died from causes other than recurrences of lung cancer were excluded from the evaluation. Deaths from other causes were evenly distributed in both groups: nine in the cyclophosphamide treatment group and eight in the control group. Of 86 patients in the treated group, 58 (68%) had local recurrences or metastases, and 54 (63%) died from spread of lung cancer. In the control group, 42 of 86 patients (49%) had recurrent disease and 34 (39%) died from cancer. Four patients in the treated group and eight patients in the control group are living with metastatic cancer as of October 1, 1972. The differences in both recurrence and death rates are statistically significant.[5]

In figure 1, the cumulative recurrence rate during an overall observation period of 5½ years is drawn for both groups according to the life-table method. Only recurrence rate was chosen for evaluation because it was felt that this is the most valuable criterion for judging the effect of adjuvant chemotherapy; survival as a whole may be influenced by additional therapy after recurrence. (This therapy was not standardized.)

During the whole period of observation there were always more recurrences in the cyclophosphamide-treated group than in the control group, especially during the first 18 months of cyclophosphamide therapy. The divergence of the two curves is less after 18 months.

Not only were there more recurrences in the treated group, than in the control group, but also significantly shorter median intervals between operation and recurrence. This is demonstrated in table 3. The median time to recurrence was 10.5 months in the cyclophosphamide-treated group and 18.5 months in the control group; the median time from operation to death was 15.7 months in the treated group and 24.5 months in the control group. This is reflected in a shorter median time from recurrence to death in the treated group (2.5 months) than in the control group (5.5 months). In figure 2, recurrences in both groups are given for each year after operation and expressed as a percentage of the total recurrences. In the cyclophosphamide-treated group, most recurrences occurred during the first year (57%). In the control group, recurrences were much more evenly distributed between the first and the second year (38% during the first year, and 33% during the second year).

[5] For the difference in recurrence rate: $\chi^2 = 6.11$; $0.05 > P\chi^2 > 0.01$. For the difference in death rate: $\chi^2 = 9.3$; $0.01 > P\chi^2 > 0.001$.

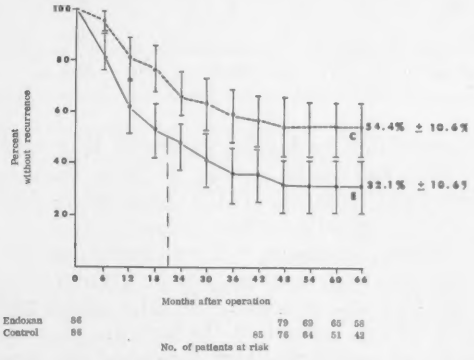


FIGURE 1.—Cyclophosphamide (Endoxan) adjuvant study: cumulative incidence of recurrences of disease (life-table method).

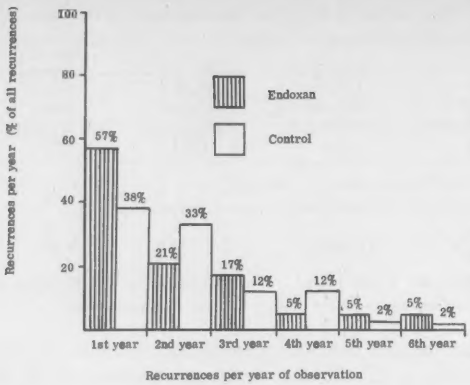


FIGURE 2.—Cyclophosphamide (Endoxan) adjuvant study: recurrence of disease in treated and control patients.

TABLE 3.—Adjuvant cyclophosphamide study: median time to recurrence of disease and death

Group	Median time (mos) from—		
	Operation to recurrence	Operation to death	Recurrence to death
Adjuvant cyclophosphamide treatment	10.5	15.7	2.5
Control	18.5	24.5	5.5

Figure 3 shows the cumulative incidence of deaths after recurrence was observed. Patients in the cyclophosphamide-treated group died in a shorter period after recurrence than did those in the control group. Nevertheless, six patients in the cyclophosphamide-treated group lived with recurrence for more than 12 months, and three patients lived for more than 24 months; in the control group, ten of the 42 patients with recurrence lived for more than 12 months with recurrent disease, and three patients lived for more than 24 months. It is difficult to explain why patients treated with cyclophosphamide died more rapidly even after recurrence when they had not received further treatment with cyclophosphamide.

No factor other than cyclophosphamide treatment could be detected by careful analysis to explain the unfavorable results in the

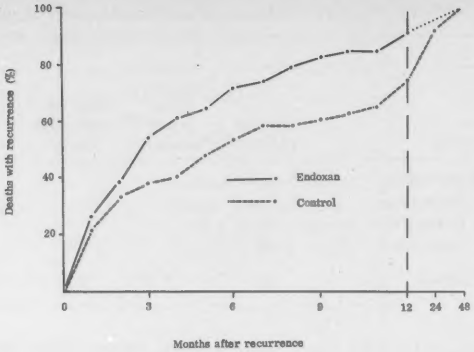


FIGURE 3.—Cyclophosphamide (Endoxan) adjuvant study: cumulative incidence of deaths after recurrence of disease.

treated group as compared with the results in the untreated control group. The age distribution in both groups (shown in table 4) was similar.

TABLE 4.—Adjuvant cyclophosphamide study: distribution of patients according to age group

Age group (yrs)	No. of patients treated with cyclophosphamide	No. of control patients
>70	9	11
60–69	41	42
50–59	28	24
40–49	7	9
<40	1	0
Median (yrs)	61.9	62.4

Distribution by histologic type of lung cancer also was quite similar in both groups. Forty-eight percent of the patients in the group treated with cyclophosphamide had differentiated squamous cell carcinoma versus 54% in the control group; for both groups together this type accounted for 51% of all patients. Thirty percent of the patients in each group had undifferentiated squamous cell carcinoma; the percentage for this type for all patients is 31%. Eight percent in the cyclophosphamide treatment group and 7% in the

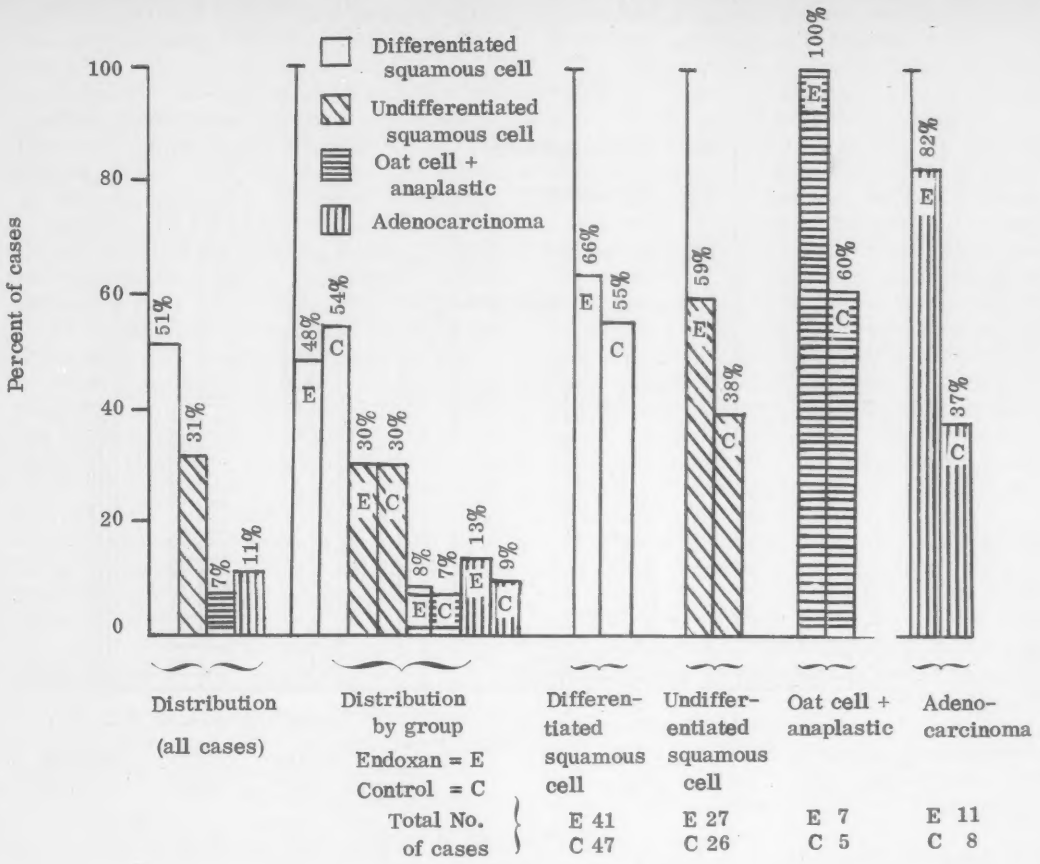


FIGURE 4.—Cyclophosphamide (Endoxan) adjuvant study: distribution by histologic type and rate of recurrence with each histologic type.

control group had a histologic diagnosis of oat cell or anaplastic carcinoma (7% of all patients in both groups), and 13% in the treated group versus 9% in the control group proved to have adenocarcinoma (11% of both groups together). Figure 4 also demonstrates the rate of recurrence with each histologic type. There were more recurrences for all histologic types in the treated group than in the control group. The difference was greater for oat cell/anaplastic carcinoma and adenocarcinoma than for the more differentiated forms. In the cyclophosphamide-treated group, 100% of the patients with oat cell or anaplastic carcinoma had recurrences, whereas in the control group, only 60% of the patients with these diseases had recurrences.

The distribution according to operative procedure is presented in figure 5. Pneumonectomy was performed in 38% of the 172 patients, bilobectomy in 11%, lobectomy in 47%, and segmental resection in 4%. In the cyclophosphamide-treated group, 47% had had pneumonectomies, 7% had had bilobectomies, 41% had had lobectomies, and 5% had had segmental resections, whereas in the control group,

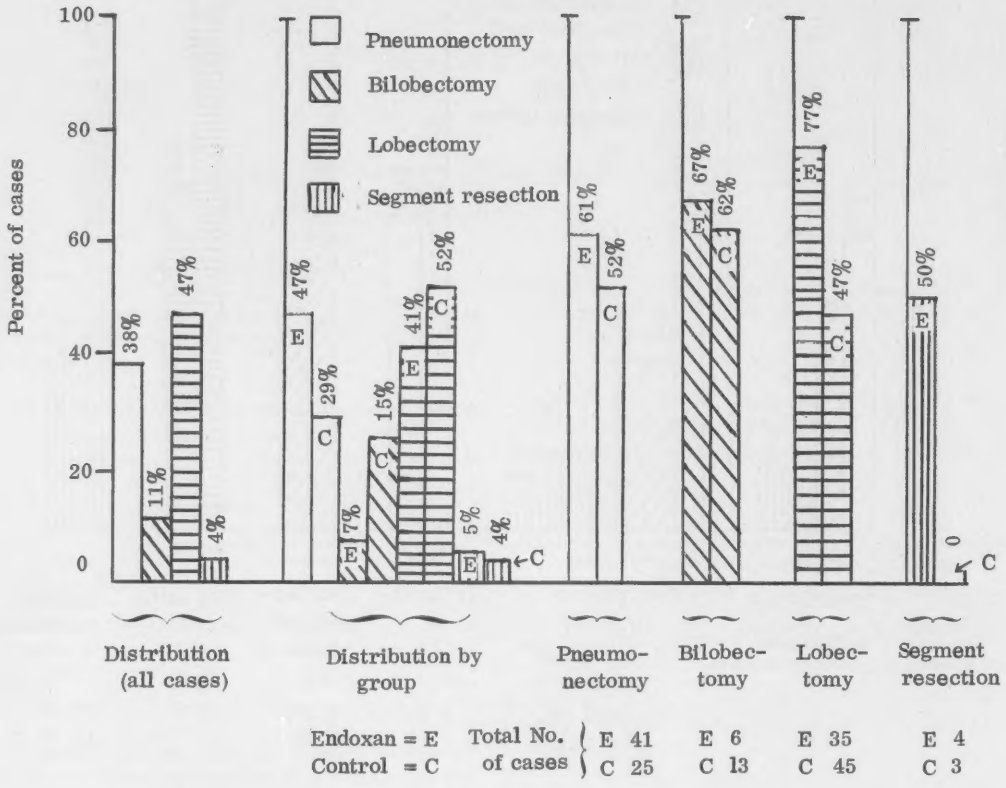


FIGURE 5.—Cyclophosphamide (Endoxan) adjuvant study: distribution by modality of operation and rate of recurrence with each procedure.

29% had had pneumonectomies, 15% had had bilobectomies, 52% had had lobectomies, and 4% had had segmental resections.

It is highly improbable that the somewhat uneven distribution by type of operation may have contributed to the unfavorable results in the cyclophosphamide-treated group, as can be seen by the rate of recurrence for each surgical procedure. Except for that in the small number of segmental resections, the difference in recurrence rate between the cyclophosphamide-treated group and the control group was greatest for the patients who had had a lobectomy and not for those who had had a pneumonectomy (77% versus 47% for lobectomies; 61% versus 52% for pneumonectomies). Lobectomy, therefore, seems to have favored recurrence in cyclophosphamide-treated patients, but not in patients in the control group, where the recurrence rate is 5% lower than in the corresponding control group with pneumonectomies (47% versus 52%).

The toxic effects of cyclophosphamide (mainly nausea and vomiting) were considerable and increased with each course of therapy. For 27% of all patients, weekly iv therapy

had to be changed to daily oral therapy, which was much better tolerated. This was done only after reduction of the dose of the weekly injections did not help to reduce nausea and vomiting. Hematologic toxicity was no problem. The mean nadirs of the white blood cell and platelet counts observed during the courses of therapy were not significantly different in patients who did or did not have recurrent disease, although the dose of cyclophosphamide was reduced more often for patients without recurrence than for patients with recurrence. In the cyclophosphamide-treated group of patients who had recurrent disease, the minus deviation from the total dose of cyclophosphamide prescribed by protocol was 1.22 g/patient, and in the group without recurrence, the minus deviation was 3.88 g/patient. Patients with recurrent disease therefore had a higher total dose of cyclophosphamide than did patients without recurrent disease. This is an additional argument for a direct relationship between cyclophosphamide treatment and higher recurrence and death rates.

DISCUSSION

Adjuvant, or "prophylactic," chemotherapy is being more and more widely used in the treatment of various carcinomas after radical operation with the intention of preventing or at least postponing recurrent disease and prolonging the patient's survival time. So far, its effectiveness has been proved in only a very few neoplasms such as Wilms' tumor (1,2), choriocarcinoma (3), and, possibly, malignant testicular tumors (4).

A number of well controlled clinical studies have demonstrated that short-term chemotherapy after radical surgical treatment of lung cancer with a single cytostatic agent has no significant effect on survival and, at certain dose levels, may increase the risk of postoperative death (1,3,5–14). Long-term adjuvant chemotherapy, therefore, seemed to be more logical and promising. Karrer (15–17) has reported some favorable effects of long-term adjuvant chemotherapy with cyclophosphamide, especially in a group of patients in whom leukopenia developed during therapy; however, Karrer's observations are not based on a strictly randomized study and his conclusions are open to criticism in several other respects.

The results of the randomized study on the effects of long-term adjuvant chemotherapy with cyclophosphamide presented here are appalling. Treatment with intermittent courses of cyclophosphamide over a period of 2 years seems to increase recurrence and death rates significantly over those observed in an untreated control group. Furthermore, the time from operation to recurrence and death in those patients who had recurrent disease, is significantly shorter in the treated than in the untreated group. No factor other than cyclophosphamide treatment has been found to explain these observations, despite a careful search for such possibilities. All data seem to favor the possibility that cyclophosphamide has a direct unfavorable effect on rate of recurrence and survival.

At the same time, these appalling results may have important theoretical and practical implications. From the theoretical point of view, it is extremely important to know that an agent such as cyclophosphamide, which has limited therapeutic effect in advanced bronchogenic carcinoma, not only is unable to eradicate tumor cells when there is minimal residual disease, but actually seems to favor the growth and propagation of residual tumor cells, possibly by some unknown effect on immunologic factors.

Furthermore, it is of interest that after 5½ years of observation the recurrence and survival curves of both groups show no tendency to converge. Since the patients were strictly randomized, it must be assumed that both the treated and the untreated groups contained a near equal number of patients who had residual viable tumor cells after "radical" operation. With time, this should produce an equal number of patients with recurrent disease and an equal number of deaths from metastatic carcinoma. The fact that this is not the case after a sufficiently long period of observation suggests that an unknown number of patients in the control group may have been able to eliminate residual tumor cells by reactivation of immunologic defense mechanisms after subradical resection. In the group treated with cyclophosphamide, this reactivation of defense

mechanisms may have been suppressed. The unfavorable effects of cyclophosphamide, therefore, may be explained by the relative failure of cyclophosphamide to kill residual tumor cells and the relative potency of the drug in suppressing the unknown host defense mechanisms or "immunologic control" reactivated in an unknown number of patients with minimal residual disease after subradical resection.

From a practical standpoint, the results of the present study caution against any uncontrolled application of cytostatic drugs after radical operation. Adjuvant chemotherapy should be used only in prospective, critically evaluated and strictly randomized studies, and probably only in the treatment of malignant diseases that are highly sensitive to the presently available cytostatic agents or combinations of such agents.

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Results of Combination Treatment of Lung Cancer Patients: Surgery Plus Radiotherapy and Surgery Plus Chemotherapy

A. Pavlov, A. Pirogov, A. Trachtenberg, M. Volkova, T. Maximov, and T. Matveeva [1]

Combination therapy for lung cancer patients is used because recurrences and metastases occur in 60%–70% of all patients within 2–3 years after radical operation. In addition, metastases to distant organs are noted in every third patient that dies within 1 month after surgery. The rationale for increasing the efficiency of surgical therapy by using adjuvant radiotherapy and chemotherapy appears beyond doubt. However, the results of the combined treatment of lung cancer are controversial.

Combination treatment in more than 600 patients with operable lung cancer has been carried out at the Moscow P. A. Herzen Cancer Institute for 13 years. For the past 4 years, patients were randomly assigned to either surgery alone, surgery and radiotherapy, or surgery and chemotherapy.

METHODS

A total of 298 patients with lung cancer were treated with a combination of surgery and radiation therapy; 86 of these patients received preoperative radiotherapy which was given daily in a single dose of 180–200 rads or every other day in a single dose of 400 rads. The total dose given was 3000–4500 rads. Surgical treatment was performed 4–6 weeks later.

A total of 212 patients received postoperative radiotherapy. The radiated region included the bronchus stump or interbronchial anastomosis, lung hilum, and mediastinum. For undifferentiated cancer both supraclavicular regions were radiated simultaneously. Radiotherapy was started within 3–5 weeks after surgery, and the daily single dose was 200 rads. The total dose was planned individually depending on the regional extent of disease observed at surgery: when there was no regional spread 4000 rads were given and when spread was present 5000–5500 rads were given.

A total of 301 patients were treated with a combination of surgery and antitumor chemotherapy used preoperatively (96 patients), postoperatively (147 patients), or both (58 patients). Sixty patients had repeated courses of treatment. The patients were operated on 1–4 weeks after the end of chemotherapy, and chemotherapy was restarted 2–4 weeks later.

Chemotherapy consisted of cyclophosphamide, 1 g given intravenously (iv) every 5 days to a total dose of 8–12 g, or thioTEPA, 20 mg given iv every other day to a total dose of 280–380 mg.[2] Half of the dose was injected preoperatively and half was injected postoperatively.

The schedules of radiotherapy and chemotherapy did not cause any difficulties at the time of surgery and did not result in postoperative complications. The high frequency of bronchopleural complications during the early part of the combined therapy study was due to the short interval between the stages of the treatment and the methods of operation.

HISTOLOGIC STUDIES

Histologic and histochemical studies of primary tumors and regional metastases after preoperative radiotherapy or chemotherapy re-

[1] Department of Thoracic Oncology, The Herzen Oncological Institute, Moscow, USSR.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

ThioTEPA: NSC-6396; CAS reg. No. 52-24-4; phosphine sulfide, tris(1-aziridinyl)-; thiophosphamide.

vealed several nonspecific changes, giving evidence of therapeutic pathomorphosis-dystrophic changes of the nucleus and cytoplasm and metadystrophic changes of the parenchyma and cancer stroma. Four stages of tumor tissue resorption were differentiated. The degree of these changes was obviously dependent upon the local radiation dose, the type of antitumor drugs, the method of administering the antitumor drugs, and the size and type of primary tumor (ie, the histologic structure).

Lesion changes were more often observed within 1–2 weeks after radiotherapy and large single doses of cyclophosphamide. These changes were in the form of dystrophic parenchymal changes accompanied by the depression of tumor cell mitotic activity, the appearance of giant cells, a decrease in the DNA and RNA content, and cell albumin coagulation.

For a period of more than 2 weeks fibroblasts spread simultaneously with the destruction and resorption of parenchymatous elements.

RESULTS

The survival time after surgical and combined treatment was studied in 616 patients that were treated from 1959 to 1969. Radiation therapy and chemotherapy combined with radical surgical treatment prolonged the survival time compared with surgical treatment only. After surgical treatment 32% of the patients survived more than 3 years and 24% survived more than 5 years; after the combination of surgery and radiotherapy 45% survived more than 3 years and 38% survived more than 5 years; and after the combination of surgery and chemotherapy 49% survived more than 3 years and 37% survived more than 5 years.

Factors in determining the effectiveness of adjuvant treatment after radical surgery include: (*a*) degree of regional spread, (*b*) metastases, (*c*) histologic structure, and (*d*) combined treatment methods.

Results of the Combination of Surgery and Radiotherapy

The combination of surgery and preoperative or postoperative radiotherapy results in remissions of long duration primarily in patients in an early stage of disease. Thus, in stages I and II the prolongation of survival time is statistically significant for all periods of observation: 66% survived more than 3 years and 56% survived more than 5 years. In stage III disease, survival is significantly better only within the first 2 years after operation.

It is statistically significant that preoperative and postoperative radiotherapy increases the survival time of patients without evidence of metastases to regional lymph nodes: 55% survived more than 3 years and 48% survived more than 5 years. After surgical operation 43% survived more than 3 years and 30% survived more than 5 years. In the cases of regional lymph node lesions, the prolongation of survival time was significantly better only for the first 3 years.

The superiority of the combination of surgery and radiotherapy over surgery alone occurs only in patients with epidermoid or undifferentiated cancer; for adenocarcinoma, radiotherapy did not significantly affect the time of survival.

Thus, radiation therapy in combination with surgery is effective in the treatment of lung cancer, especially in the early stages of epidermoid and undifferentiated cancer. Preoperative radiation therapy is not associated with an increase in postoperative complications.

Results of the Combination of Surgery and Chemotherapy

The use of antitumor drugs in combination with surgery in the treatment of lung cancer has great significance. Preoperative chemotherapy does not prolong the survival time, but postoperative chemotherapy does. The combination of preoperative and postoperative antitumor drugs is of benefit: 57% of the patients survived more than 3 years and 48% survived more than 5 years.

The effects on distant metastases appear better when chemotherapy is used for prolonged periods of time. These results need confirmation using random-allocation studies.

In stage I or II lung cancer, chemotherapy not only improves the 5-year survival rate, but also produces a significantly decreased mortality rate within the first 3 years. In our study,

the proportion of patients surviving after combined treatment gradually decreased every year by 5%–11%, while after surgery alone the highest mortality rate occurred within the first 3 years. In the first postoperative year 23% of the patients died and in the second and third years 15%–16% died. In these stages, combined treatment is superior to surgery alone for all periods. For patients with stage III cancer the improvement is significant within the first 3 years only.

The antitumor drugs have produced a statistically significant increase in patient survival in the absence of metastases to intrathoracic lymph nodes: 56% survived more than 5 years compared to 30% who survived after surgery alone. For patients with spread to regional lymph nodes the improvement is statistically significant for the first 3 postoperative years only: 89% survived more than 1 year and 30% survived more than 3 years. After surgery alone the rates were 42% and 18% respectively.

Chemotherapy has increased the survival time for patients after radical surgery for epidermoid and undifferentiated carcinoma, but it has not significantly affected the survival time for adenocarcinoma. Therefore, the use of cyclophosphamide and thioTEPA in the combined treatment of patients with adenocarcinoma is inexpedient.

COMMENT

Our experience with the combined treatment of a large number of patients gives us an opportunity to reach several basic conclusions:

1. The key to successful treatment of lung cancer is to diagnose it early. Only in stages I and II does the combination of radiotherapy or chemotherapy with radical surgery result in an increase in survival of 3–5 years.

2. Further study of combination therapy for lung cancer in stage III patients is necessary. This investigation must follow the principle of using other antitumor drugs, improving the methods of administering the existing drugs and radiotherapy, and using chemotherapy and radiotherapy in combination with surgery and repeated courses of chemotherapy.

3. Surgery remains as the basic method of treating operable adenocarcinoma patients. Antitumor preparations and radiotherapy do not affect the survival time of patients who undergo radical surgery for adenocarcinoma.

4. In our studies, adjuvant radiotherapy or chemotherapy does not result in any increase in postoperative complications or lethality.

Radiation Therapy Techniques Suitable for Intercenter Cooperative Studies of Bronchogenic Carcinoma

R. Sealy, L. M. Barry, L. F. Rapley, and P. L. M. le Roux [1,2]

It is well known that carcinoma of the lung tends to metastasize to the mediastinum and to invade this area by local extension. It is, moreover, difficult to individually assess the extent of the tumor with a large degree of accuracy in individual patients who may have relatively advanced local disease and are in indifferent general health. Diagnostic roentgenograms do not adequately show small masses in this region; there is no effective method of scanning squamous cell carcinoma with radioactive isotopes and the view obtained with mediastinoscopy is limited. This implies that in planning X-ray treatment for patients, the primary tumor and large areas of the mediastinum should be included in the treatment volume. With the availability of supervoltage X-rays and cobalt units there is usually no physical advantage in situations of this kind in using more than three ports of entry for the radiation treatment. It may indeed be disadvantageous to do this, since even a three-field arrangement with one anterior and two posterior oblique fields is likely to deliver a very substantial absorbed dose to normal lung tissue (fig 1). This increased dosage to the lung tissue is undesirable since many patients with bronchogenic carcinoma have chronic bronchitis and emphysema with considerable damage to the pulmonary function, quite apart from the disabilities produced by the carcinoma itself. A similar high dose in normal lung is likely to be achieved when an anterior mediastinal field and a posterior oblique wedged field are used (fig 2). In this situation an undesirably high dose is obtained in the normal lung posterolaterally. If this distribution is corrected for lung absorption, the situation is likely to be worse. It should also be noted that in this distribution minor inaccuracies in the placement of the fields will result in a large dose to the spinal cord.

Perhaps the best approach to treating smaller areas of involvement in bronchogenic carcinoma is the three-field technique with two anterior wedged fields and a partial posterior wedged field where necessary (fig 3). This procedure produces a satisfactory absorbed dose to the tumor, a low dose to the spinal cord, and a much smaller dose to the ipsilateral lung. When the posterior partial field is not necessary, the dose to the ipsilateral lung is further reduced. The difficulties with this approach, however, are that one may wish to irradiate a greater volume of the mediastinum and that not every case lends itself to this type of distribution. In addition, it may be difficult to localize the tumor and the planning must always be individual. Under these circumstances this approach does not lend itself well to comparison from case to case and center to center.

The implication, therefore, is that anterior and posterior opposing fields should be used with their margins carefully tailored to include the known and likely tumor volume and a minimal margin of uninvolved lung tissue. This approach is likely to eventually produce rectangular L-shaped or T-shaped fields when the primary growth is included in the treatment volume.

In contrast to the likelihood of lung damage with multiple oblique fields of any substantial size, the limitation in the opposing-field arrangement is the dose to the spinal cord. The arrangement of two opposing fields is shown in figure 4. It can be seen that when no lead screening is used the spinal cord receives a dose that is at least as great as the tumor dose. If a lead strip (1 cm wide and 5 cm thick) is used posteriorly throughout the treatment, the dose

[1] Department of Radiotherapy and Department of Bio-Engineering and Medical Physics, Groote Schuur Hospital, and the University of Cape Town, South Africa.

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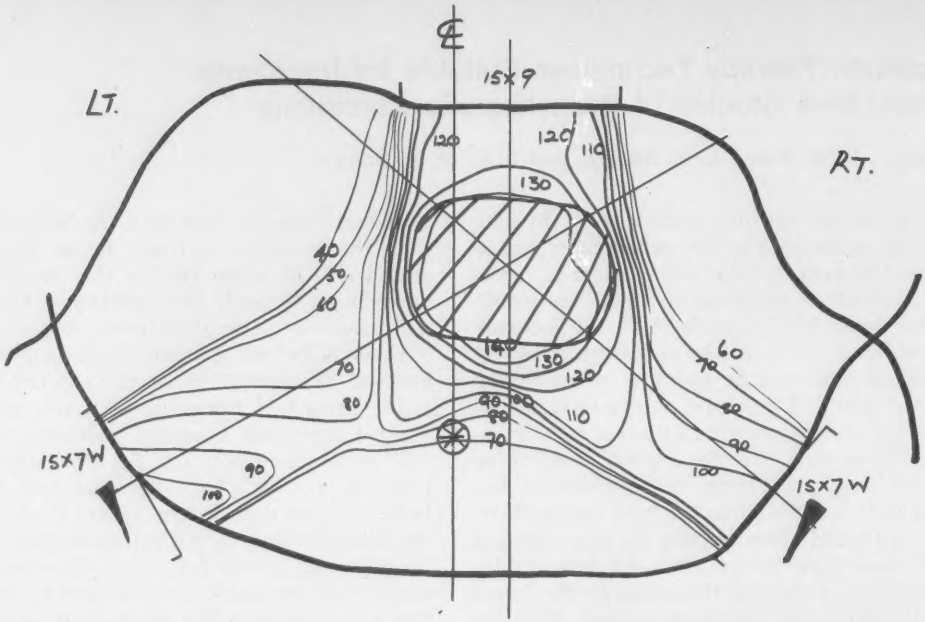

FIGURE 1.—Three-field technique for radiation treatment of bronchogenic carcinoma (one anterior and two posterior oblique fields). (All curves shown have been plotted on a Toshiba Automatic Isodose Plotter Model MRA-301 in the x and y axes. For the sake of simplicity only the major patient contours have been shown. All plots are shown with full tissue compensation but with no correction made for lung transmission. The position of the spinal cord is shown by an asterisk in all plans. The machine used was an Eldorado 8, 1.5-cm diameter source at 80 cm source-skin distance.)

to the spinal cord drops to about 50% and instead of a tumor-spinal cord ratio of 90:100 with the unleaded fields, the tumor-spinal cord ratio is in the worst instance 70:50. A similar situation exists in cases of narrower separation of the opposing fields (fig 5). In this instance it will be seen that the spinal cord-tumor ratio with unleaded treatment would be 130:120, whereas the ratio with a lead strip used centrally posteriorly is in the worst case 80:100.

The situation is not improved, and may indeed be made worse, by partial leading of the spinal cord posteriorly (figs 6 and 7). With a 16-cm separation (fig 6), spinal cord-tumor ratio shows a worse situation, with a minimum tumor dose of about 100 and a spinal cord dose of about 95. The same situation results with partial leading at a greater separation of 25 cm (fig 7).

It is therefore suggested that a reproducible and reliable method of treating locally advanced lung cancer would be the two-opposing-field technique using a 1-cm lead strip over the spinal cord of the posterior field throughout the entire course of treatment with the fields centered over the spine. However, when the centers of the fields are displaced from the midline of the patient by 2 cm or more, it becomes advantageous to use partial leading over the spinal cord posteriorly (fig 8). It can be seen here that with two-thirds leading, a spinal cord-tumor dose ratio of 70:100 is obtained. The objection to this distribution might well be that when compared to the anterior three-field technique already mentioned, once again a significant dose builds up in the ipsilateral uninvolved lung tissue.

The situation is not improved by using a

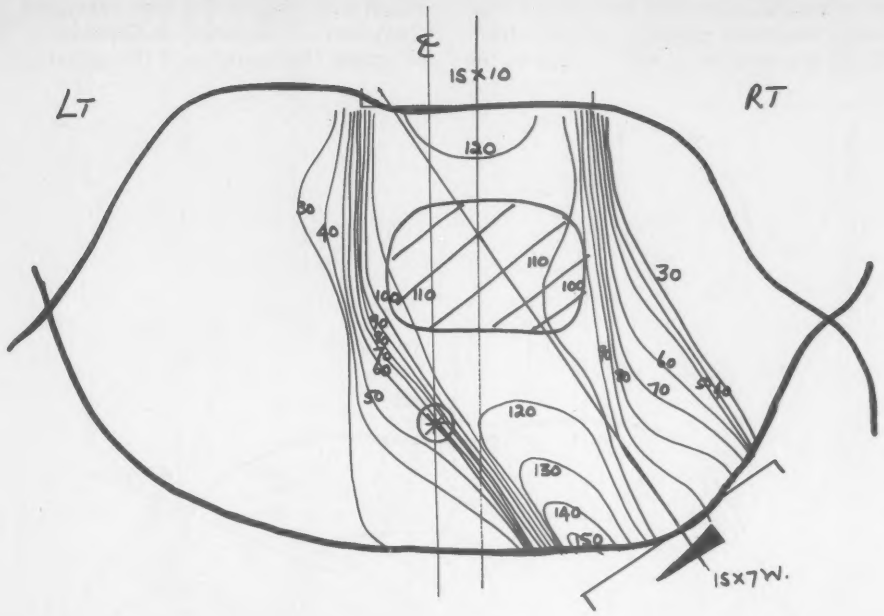

FIGURE 2.—Two-field technique for radiation treatment of bronchogenic carcinoma (an anterior mediastinal field and a posterior oblique wedged field.)

three-field technique with two wedged fields posteriorly (fig 9). With this technique, the absorbed dose in the ipsilateral normal lung tissue remains high and a significant absorbed dose accumulates in the contralateral lung tissue posteriorly. The ratio between the tumor dose and the spinal cord dose remains the same.

Although we do not have sectography available in our Department, it is felt that the information obtained from this type of procedure may allow reduction of the dose to the normal lung tissue by individualized planning. Sectography, however, is unlikely to be available in many centers that are taking part in cooperative studies.

A further difficulty is the uncertainty of the pentration of the beam due to the interposed lung tissue. This might be computed more accurately from sectography photographs if they could be effectively related to the density of the tissue shown.

Transmission measurements taken at the center of the emergent beam on the contralateral chest wall are, in our opinion, unsatisfactory since they only reveal the total absorption that the beam has undergone and they do not give us information as to what is happening within the chest. An improvement in the situation might possibly be obtained by measuring in individual patients the absorbed dose within the esophagus using lithium fluoride capsules, for example. This procedure is limited in application, however, since with multiple planned fields the beams may indeed miss the esophagus or the esophagus may be in an area of steep dose gradient making this technique unsatisfactory and unreliable. This approach would, however, lend itself to the assessment of treatment with two opposing fields, where the esophageal dose and the exit doses for both fields could be measured. In this case there would be some degree of individual control.

It is therefore suggested that multiple in-

tercenter comparative studies involving radiation should, whenever possible, utilize a technique of two opposing fields with leading of the spinal cord where the dose necessary for the treatment of the tumor is likely to be equal to or exceed the tolerance of the spinal cord.

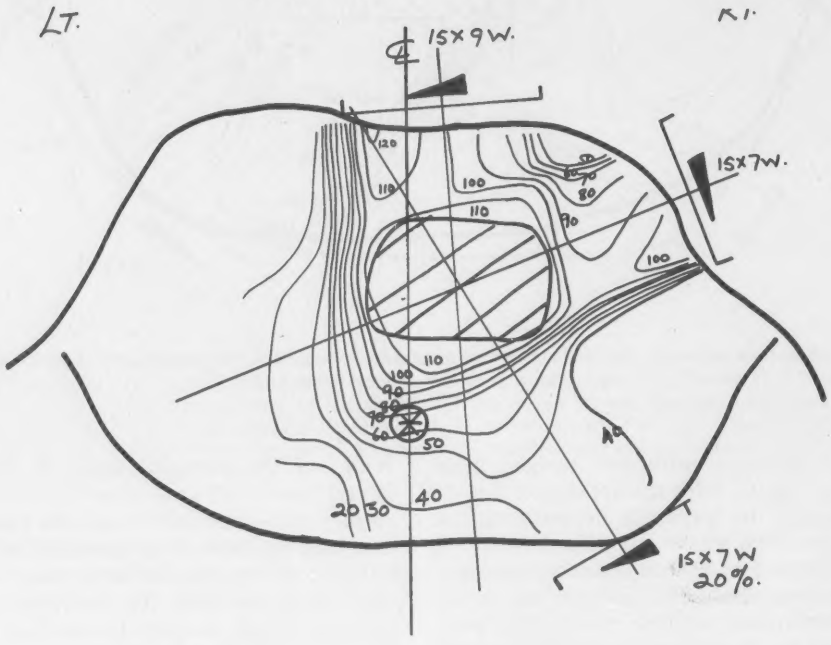

FIGURE 3.—Three-field technique for radiation treatment of bronchogenic carcinoma (two anterior wedged fields and a partial posterior wedged field.)

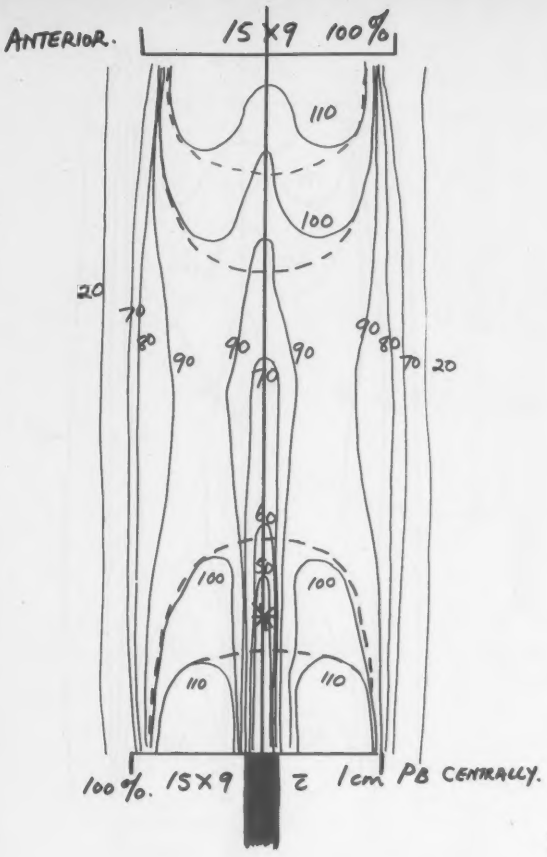

FIGURE 4.—Two opposing fields for radiation treatment of bronchogenic carcinoma. ------ = Unleaded treatment; ——— = leaded treatment on posterior field only (separation, 25 cm).

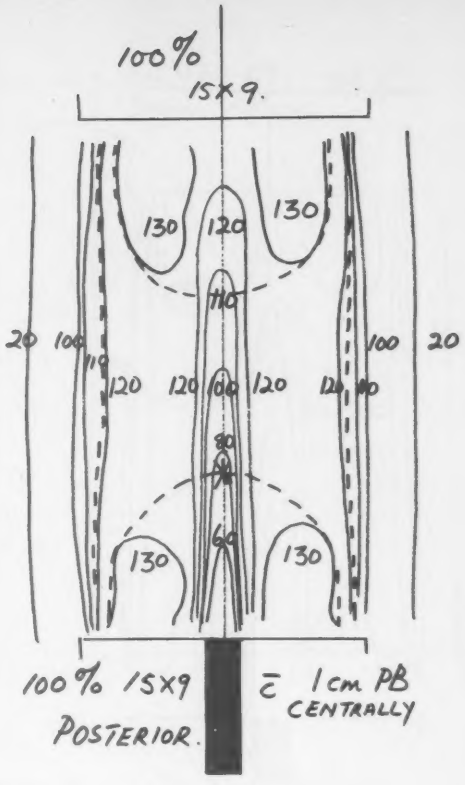

FIGURE 5.—Two opposing fields for radiation treatment of bronchogenic carcinoma (separation, 16 cm). ------ = Unleaded treatment; ——— = leaded treatment.

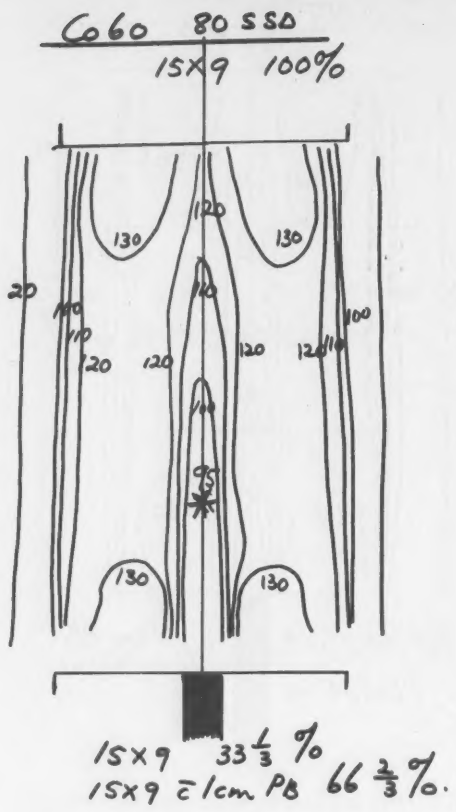

FIGURE 6.—One-third leading of the spinal cord posteriorly with a 16-cm separation.

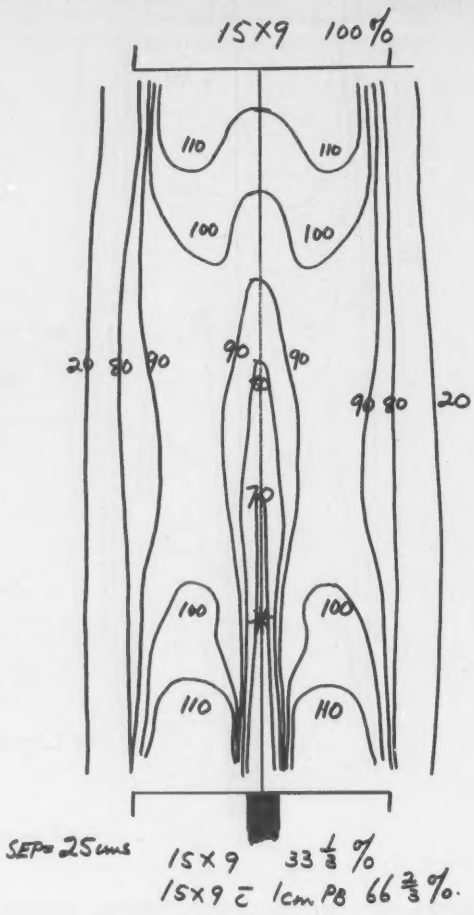

FIGURE 7.—One-third leading of the spinal cord posteriorly with a 25-cm separation.

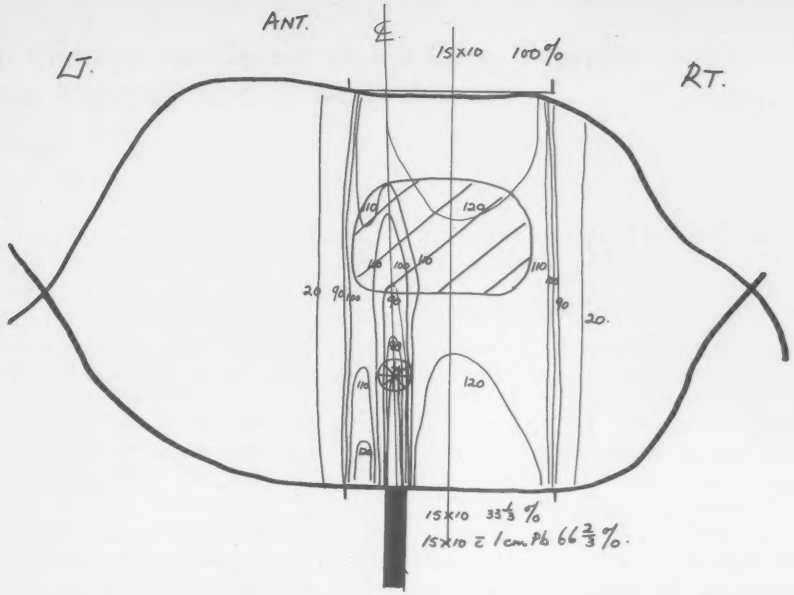

FIGURE 8.—Partial leading (two-thirds) over the spinal cord posteriorly, used when the centers of the fields are displaced from the midline of the patient.

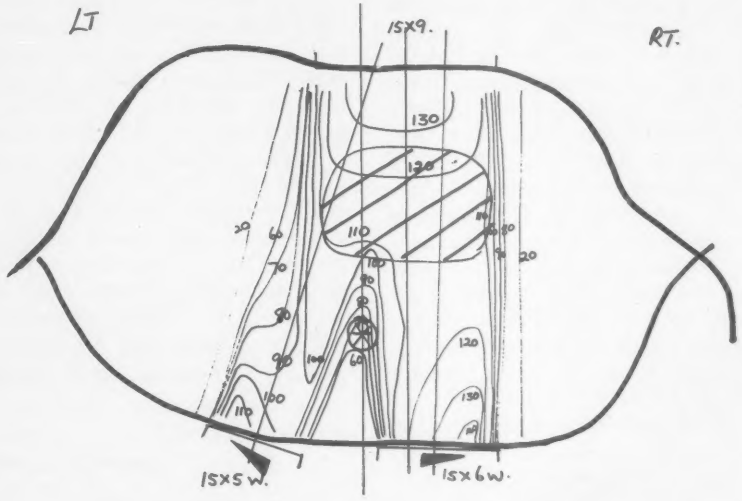

FIGURE 9.—Three-field technique with two wedged fields posteriorly.

Radiation Therapy for Cancer of the Lung: Previous Experience and Definition of Current Issues

Carlos A. Perez [1]

According to estimates of the American Cancer Society, 72,000 new cases of bronchogenic carcinoma will be seen in the United States in 1973 (1). Bronchogenic carcinoma is a highly lethal disease; only approximately 5% of all affected patients survive more than 5 years. A marked increase in the incidence of this disease has been noted over the past 30 years (1,2), although some authors believe that this may level off in the not-too-distant future (3).

Early diagnosis is accomplished in only a few cases, and it is only in this population of patients that surgical resection has been moderately successful in controlling the disease. Five-year survival rates in this group are about 50%.[2] Radiation therapy has proved to be of limited value in prolonging survival and, on occasion, in producing a long-term cure (4–6). The main reasons for the failure to control the disease by using surgery or radiation therapy are the inability to eradicate the local tumor or intrathoracic dissemination and the high incidence of distant metastases (7). The tendency of bronchogenic carcinoma to disseminate has been correlated with the histologic nature of these tumors. This tendency is more frequent in undifferentiated lesions, oat cell carcinoma, and adenocarcinoma than in squamous cell carcinoma (8,9).

It is the purpose of this paper to analyze the various facets of the problem of treating bronchogenic carcinoma, since despite the voluminous literature on the subject, a number of questions remain unanswered.

[1] Division of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo.

[2] Working Party on Cancer of the Lung, Report of the NCI-VA Report of Surgical Committee, Feb 1972.

PATIENTS WHO MAY BENEFIT FROM RADIATION THERAPY

Squamous Cell Carcinoma

Little improvement in the prognosis of squamous cell carcinoma has been achieved despite the great technical advances in radiotherapy and the increased knowledge of the biology of lung cancer in the past 30 years.

Operable and resectable lesions.—It is known that surgical procedures (lobectomy or pneumonectomy) may yield 2-year survival rates of about 50% in patients with tumors which are localized to the primary site without nodal metastasis, and 20% in patients with hilar node metastasis.[2] Smart (10,11) reported a 22% 5-year survival rate in a carefully selected group of 40 patients with early bronchogenic carcinoma who were given doses of 5000–5500 rads over 7–8 weeks (patients with squamous cell carcinoma) or 4900–5500 rads (patients with anaplastic tumors). These results were comparable to those of some surgical series. Morrison, Deeley, and Cleland (12) carried out a prospective randomized study of 58 patients with bronchogenic carcinoma which was confined to the thorax without gross evidence of distant metastasis. These patients were treated with either surgery or supervoltage irradiation (8 Mev X-rays). Of 20 patients surgically treated for squamous cell tumors, 30% survived 4 years, whereas only one of 17 patients (6%) who were treated with radiation therapy survived for the same period of time. Patients with anaplastic lesions showed no significant difference in survival rate after either method of treatment. The dose of radiation was only 4500 rads administered over a period of 4 weeks, which is considered inadequate for the sterilization of squamous cell carcinoma.

Unresectable tumors.—Guttman (5) reported on a group of 103 patients whose tumors were unresectable at thoracotomy and who were subsequently treated with 2 Mev X-rays to a tumor dose of 5000 rads administered over a 5-week period. Survival rates were 57.2% for 1 year, 17.4% for 3 years, and 8.7% for more than 5 years. The average survival time of these patients was raised to 27 months as compared with 6 months for the untreated patients reported in the literature.

Inoperable tumors.—Guttman (5) reported on 150 patients with microscopically confirmed inoperable lung cancer treated with 2 Mev X-rays to a dose of 5000 rads administered over approximately 5 weeks. Forty percent of these patients were alive for more than 1 year after the completion of treatment, 13% survived for 2 years, and 7% survived for 3 years.

Roswit et al (6) reported a 22.2% survival rate at 1 year in a group of 308 patients with inoperable tumors who, in the majority of the cases, were treated with orthovoltage X-rays to dose levels of 4000–5000 rads. In the same study a group of 246 controls given an inert placebo had a 16% survival rate at 1 year.

Disseminated disease.—Although it is the clinical experience of many radiation therapists that irradiation may produce palliative effects in patients with cough, hemoptysis, fever due to recurrent pulmonary infection, pain, respiratory insufficiency due to atelectasis, and superior vena cava syndrome, no significant prolongation of life has been observed in patients with disseminated tumors.

Oat Cell Carcinoma

Miller et al (13) reported on a group of 144 patients with oat cell carcinoma of the lung: 71 patients were randomly assigned to surgical therapy and 73 to radical radiation therapy. In 34 of the 71 patients in the surgical group, a pneumonectomy was performed; radical radiation therapy was given to 62 of the 73 patients in the irradiation group. Three of the 73 irradiated patients survived for 5 years (4%) as compared to only one patient in the surgical group who was inoperable and received palliative radiation therapy instead of surgery. He survived for 60 months and was the sole survivor of the surgical series. Metastasis, the most common cause of failure, was noted in 81% of the 71 surgical patients and in 91% of the 73 irradiated patients.

No reliable information is available on the potential benefit of radiation therapy in prolonging the lives of patients who have widespread tumor dissemination at the start of treatment.

Other Histologic Types

Even though some investigators feel that adenocarcinoma and large cell anaplastic carcinoma are not particularly sensitive to irradiation,[3] others have reported no significant difference in the radiation response or the survival rates in these patients compared to patients with squamous cell and oat cell carcinoma.

MOST EFFECTIVE DOSE OF RADIATION IN THE TREATMENT OF BRONCHOGENIC CARCINOMA WITH AN ACCEPTABLE LEVEL OF EFFECTS ON NORMAL TISSUES

Bromley and Szur (14) demonstrated that localized lung cancer can be destroyed in about 40% of the cases with orthovoltage radiation at moderate dose levels (average, 4700 rads). Several authors, among them Guttman (5), Rubenfeld and Kaplan (15), and Rubin et al (16), have correlated higher tumor doses with better survival rates. Admittedly, a certain degree of selection exists in a number of these patients, with the most favorable cases receiving the higher doses.

In contrast, Roswit et al (6) failed to observe a difference in the survival of patients who received doses of over 5000 or 6000 rads as compared with others treated at lower dose levels. This lack of difference was observed in patients who received less than 4000 rads and in those who died within the first 2 months following therapy.

Bloedorn et al (17) reported that in a group of 26 patients who received 6000 rads to the chest preoperatively over a 6-week period, careful study of multiple sections of operative

[3] Working Party on Cancer of the Lung, Report of the NCI-VA, unpublished data.

specimens showed no recognizable tumor cells in the primary site in 54% of the patients or in the mediastinal lymph nodes in 92%.

Rissanen et al (18) analyzed 67 patients who had histologically verified inoperable lung cancer. In 18 patients who received tumor doses between 4800 and 6250 rads over 5–10 weeks, no evidence of carcinoma was found in the treated area. In contrast, 26 patients who showed clearly viable carcinoma in the treated area had received doses of only 2000–3000 rads. Twenty-four patients with cancer of the lung were preoperatively irradiated 4–6 weeks prior to surgery. A tumor dose of 5500–6000 rads was given in 5½–6 weeks. Seven patients showed no evidence of any residual primary tumor, and of 15 patients with preoperative radiographic evidence of hilar or mediastinal adenopathy, only three showed residual neoplasm on microscopic sections.

Of interest is the report by Deeley (4) which described higher survival rates in a group of 51 patients receiving 3000 rads in 20 sessions over a period of 4 weeks as compared to a group of 51 patients treated with 4000 rads in the same number of sessions and weeks. The survival rate was 6% at 2 years in the 3000-rad group as opposed to no survivals in the 4000-rad group. It was felt that this was probably due to a greater incidence of fibrosis developing in the patients treated with higher doses. There was no significant difference in the incidence of distant metastases or residual intrathoracic carcinoma in the two groups.

OPTIMAL FRACTIONATION SCHEDULE IN IRRADIATION OF BRONCHOGENIC CARCINOMA

Most of the patients with bronchogenic carcinoma treated with radiation receive continuous courses of therapy. A few authors have explored the potential of the split-course radiation therapy, most of them with an economic advantage viewpoint in mind; however, it is known that some radiobiologic principles which include the re-oxygenation of initially hypoxic tumor cells, the reduction of tumor mass resulting in improved vascularization and better repair of normal tissues may be strong arguments to support this type of irradiation (20, 21).

Levitt et al (22) reported no difference in symptomatic relief or in survival rate in a group of 15 patients who were randomly assigned to the split-course therapy (consisting of three doses of 600 rads each delivered on 3 consecutive days and repeated 28 days later) and a group of 14 patients who received daily fractionated radiation therapy to a total dose of 6000 rads given over 6–8 weeks. Dutreix et al (23) reported satisfactory palliative results with a regimen consisting of two doses of 1650 rads each given over 48 hours. After 3 weeks rest, nine fractions of 300 rads each were given three times weekly. Deeley (4) has conducted a comparative trial of twice weekly irradiation, at dose levels of 2400 rads over 28 days for anaplastic tumors (eight fractions of 300 rads) or 3200 rads in 28 days (eight fractions of 400 rads) for squamous cell carcinoma. Another group of patients received five fractions per week (3000 rads in 28 days for anaplastic tumors and 4000 rads in 28 days for squamous cell carcinoma). No difference in survival, morbidity, or metastatic spread has been found in the preliminary analyses of the 2-year experience.

On the other hand, Abramson and Cavanaugh (24) reported a significantly better survival rate (43% at 1 year) in a group of patients treated with a 2000-rad tumor dose divided into five fractions in 1 week followed by 3 weeks rest and 2000 rads given in a similar fashion after the rest. A 14% 1-year survival was observed in the control group, treated with 6000 rads over 6 weeks in five fractions per week. However, further analysis of this data with longer followup shows a lesser difference in the survival curves at 2 and 3 years.[4] Holsti and Vuorinen (25) have employed the split-course therapy in two regimens: (*a*) 5000–6000 rads over 5–6 weeks in a continuous course (six fractions per week), and (*b*) 5%–10% more dosage than in (*a*) with an additional 2–3 weeks overall time interposed between the fractions. For the patients who were treated with the split-course therapy, the survival rates were slightly higher at 6 months (70%) than at 1 and 2 years

[4] Abramson N. Personal communication, May 1972.

(35% and 10% respectively) in contrast to the patients who were treated by continuous irradiation (54%, 33%, and 4% survival at 6 months, 1 year, and 2 years respectively).

Rissanen et al (18) described a higher incidence of tumor sterilization in a group of 38 patients on whom postmortem examination was performed after the megavoltage split-course irradiation treatment (6000–7000 rads). Fourteen of the 38 patients (37%) treated with this regimen had complete microscopic destruction of the tumor whereas only four of 29 patients treated with comparable continuous irradiation (14%) showed no tumor in the treated area. The incidence of distant metastasis in the split-course group was 76% in contrast to 93% in the continuous group.

Effects of Irradiation on Pulmonary Function

It is well known that fractionated doses of radiation over 2500 rads may produce permanent damage to the alveolar endothelium and induce interstitial fibrosis of the lung parenchyma (26). It must be remembered that a large proportion of these patients are lifelong smokers with chronic obstructive lung disease (27,28). Germon and Brady (28) studied a group of 30 patients with bronchogenic carcinoma who received doses of about 6000 rads in 5–6 weeks. Prior to treatment, the pulmonary function tests showed some abnormality in all of the patients, and most of the patients had some degree of obstructive lung disease. Other findings included increased residual volumes greater than 40% of the total lung capacity, abnormal distribution of alveolar ventilation, and reduced diffusing capacity for CO_2. Severe respiratory disability attributable to radiation pneumonitis and fibrosis did not develop in any patients. Decreased vital capacity and diffusing capacity was observed after irradiation as well as significant alterations in pulmonary arterial perfusion. These were demonstrated prior to therapy in areas larger than those radiographically suspected, but greater impairment was noted after irradiation and this was probably due to capillary damage resulting in decreased perfusion.

Teates and Cooper (29) reported on 16 patients who were followed for 40 months after thoracic irradiation. Twenty-five percent showed definite evidence of ventilatory function reduction and 50% showed radiographic findings that were consistent with radiation effect in the lung. Since this sequelae must be expected after radical irradiation of the lung, it is imperative to definitely establish that the benefits of irradiation will outweigh these undesirable effects on an already impaired pulmonary function. Likewise, the minimal volume to be treated should be accurately determined and careful treatment planning computations are necessary to determine the dose which will yield the best therapeutic results with a minimum of complications.

RADIATION THERAPY COMBINED WITH SURGERY COMPARED WITH EITHER MODALITY ALONE

Preoperative Irradiation

Several randomized studies have been reported evaluating the potential usefulness of preoperative irradiation in the treatment of cancer of the lung. None of the reports have shown significant benefits in terms of survival or tumor control except for those dealing with the rare apical lung cancer (Pancoast's tumor) (17,30,31). Paulson et al (32) and Hilaris et al (33) have observed 3–5-year survival rates of about 30% in selected groups of patients with apical tumors that were treated with moderate dose levels of preoperative irradiation (3500–4000 rads in 3–4-week periods) followed by en bloc resection of the tumor alone (32) or combined with interstitial irradiation (33).

Postoperative Irradiation

Postoperative irradiation can only be expected to inhibit the growth of microscopic deposits of tumor or residual growth in the hilar and mediastinal nodes. Postoperative irradiation would not affect the already disseminated foci outside these volumes which may not be clinically apparent at the time of surgery.

Several studies with relatively small groups of patients have failed to show any significant improvement in the survival time of patients surgically treated for bronchogenic carcinoma

and irradiated postoperatively. Bangma (34) reported on 73 patients who were randomly assigned to one of two groups after pneumonectomy: one group (36 patients) received postoperative irradiation; the other group (37 patients) served as the control. A dose of 4300–4500 rads was usually given over approximately 5 weeks. The two groups did not significantly differ in the number of deaths or the frequency of tumor metastases. A higher death rate within the first postoperative year was noted among the irradiated patients (six deaths among eight patients) than among the controls (one death among six patients). In addition, no survival difference was noted between the patients treated by lobectomy and those treated by pneumonectomy. It is noteworthy that in only two of eight patients treated by lobectomy who received postoperative irradiation, did intrathoracic metastases develop, whereas six had extrathoracic tumor dissemination. In the nonirradiated control group, intrathoracic metastases developed in five patients and only one had extrathoracic tumor dissemination.

VALUE OF PROPHYLACTIC IRRADIATION OF POTENTIAL AREAS OF TUMOR SPREAD

Nohl (35) has published a comprehensive analysis on the pattern of spread of bronchogenic carcinoma to the hilar and mediastinal lymph nodes. The nodal involvement is approximately 40% in patients with squamous cell carcinoma as opposed to 80%–90% in patients with oat cell or undifferentiated carcinoma. The adenocarcinomas and large cell undifferentiated lesions seemed to have a high incidence of lymph node involvement which is similar to that of the anaplastic lesions (8,35). In a group of 680 postmortem examinations of patients with bronchogenic carcinoma, Line and Deeley (8) reported a high incidence of metastatic lesions to the lymph nodes, liver, adrenals, bone, and brain. Metastases were almost twice as frequent in patients with oat cell carcinoma, anaplastic carcinoma, and adenocarcinoma than in patients with squamous cell carcinoma.

Bell (36) noted metastasis in 17 of 88 patients with known bronchogenic carcinoma on whom abdominal laparotomies had been performed (19.3%). In most cases the metastasis was to the liver (12 patients) or to the lymph nodes in the upper abdomen (three patients).

Since there may be a centrifugal distribution of metastasis in lung cancer, as suggested by Onuigbo (9), the greater the distance between the organ and the primary pulmonary growth, the less the probability of metastasis developing. If there is an orderly pattern of dissemination, it would be theoretically useful to prevent the development of metastatic deposits in these areas of high risk. Also, since the majority of the chemotherapeutic agents do not cross the blood-brain barrier, the central nervous system must be considered a sanctuary for tumor cells which would not be affected by circulating chemicals. Therefore, prophylactic irradiation of the brain should be tried in special groups of patients, such as those with oat cell carcinoma. This approach has proved to be effective in children with acute leukemia.

IMPROVEMENTS IN SURVIVAL USING RADIATION THERAPY IN BRONCHOGENIC CARCINOMA

Radiation therapy remains the mainstay for palliation of patients with limited disease. About 75% of the patients treated showed significant tumor regressions with doses over 4000 rads (5,15). In some studies, the treated patients survived about 20% longer than the untreated controls (6).

In an analysis of the controversial status of the management of lung cancer, Rubin (16) pointed out that researchers are obsessed with the length of survival when reporting the results in the treatment of bronchogenic carcinoma, rather than determining the local or regional control of thoracic disease and the quality of survival.

As stated previously, there are conflicting reports in the literature as to whether irradiation prolongs the survival of patients with cancer of the lung. Some randomized studies have shown minimal or no improvement in the survival time of irradiated patients even after the addition of chemotherapeutic agents. This has been reported by Roswit et al (6) (radiation alone), Kraft et al (37) (radiation

and mechlorethamine compared with radiation alone or mechlorethamine alone), and Durrant et al (38) (no treatment, irradiation alone, or irradiation combined with mechlorethamine).[5] When skillfully administered, radiation therapy can be quite effective in palliating the distressing symptoms of these patients, but whether this prolongs their useful life or not remains to be definitely demonstrated.

BENEFITS OF ADJUVANT THERAPY

The roles of chemotherapy and immunotherapy in the management of carcinoma of the lung will be extensively reviewed in this Workshop. Over the past 20 years, numerous prospective and nonrandomized studies have explored the potential benefits of chemotherapeutic agents in the treatment of bronchogenic carcinoma. Multiple trials with single agents, including mechlorethamine, vinblastine, cyclophosphamide, actinomycin D, 5-fluorouracil, and hydroxyurea,[6] have failed to show any improvement in survival time or tumor control (2,37, 39–45).[7] Bergsagel et al (46) reported a slight prolongation of survival in a group of patients who received repeated doses of cyclophosphamide combined with irradiation, as compared with a control group of patients who were treated with irradiation alone. Only a few drugs, alone or in combination, have shown an increased survival, particularly in patients with oat cell and anaplastic tumors (47).[8]

The potential therapeutic value of combining several chemotherapeutic agents or stimulating the immune response of the patient as an adjuvant to surgery or radiation therapy remains to be explored.[9,10]

CONCLUSIONS

In spite of numerous clinical trials, the management of patients with bronchogenic carcinoma remains a formidable challenge with a myriad of unresolved issues. Except for selected patients with very small peripheral tumors, few patients can be saved, even when the disease is diagnosed in an asymptomatic stage (48). In addition to a relatively high incidence of local or lymph node recurrence after surgical treatment or irradiation, the frequent development of distant metastases compounds the problem.

The role of radiation therapy in the integrated management of bronchogenic carcinoma remains to be established. Prospective clinical trials will be necessary to identify particular target groups of patients who may potentially benefit from this modality of treatment, and careful analysis will be required to determine the optimal parameters of irradiation which will yield the highest cure rates with an acceptable degree of morbidity. Pathologic examination of irradiated tumors and lymph nodes may contribute to this knowledge. Thorough postmortem examinations may shed light on the natural history of the disease, particularly if some prolongation of life is achieved by affecting the growth rate of the intrathoracic tumor, even if the patient is not cured. The interrelationship between irradiation, surgical treatment, chemotherapy, and immunotherapy must be carefully investigated, and the effects of irradiation or drugs on the immune response of the patient should be evaluated.

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[6] Vinblastine: NSC-49842; CAS reg. No. 6449-03-2; vincaleukoblastine, sulfate (1:1), monohydrate.

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

Actinomycin D: NSC-3053.

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8.

Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1.

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Radiotherapy for Bronchogenic Carcinoma: Actual Difficulties and Plans for the Future

M. Dana [1]

SUMMARY

The general results of radiotherapy in patients with bronchogenic carcinoma are very poor. Some data strongly suggest that even squamous cell carcinoma must be considered and treated as a systemic disease. Rather than increasing the dose of radiation, which may cause considerable after effects on the mediastinum, we suggest the use of systemic treatment (eg, chemotherapy and/or immunotherapy) and perhaps prophylactic irradiation of common sites of metastasis as an adjuvant to surgical treatment or radiotherapy.

[Cancer Chemother Rep Part 3, vol 4:153–155, 1973]

Although considerable work in radiotherapy has been done in different countries with various modalities, the results are poor. For many people, especially specialists and general practitioners, the question arises of the usefulness of radiotherapy (and other treatments) for inoperable bronchogenic carcinoma. For this reason, the number of patients we treat in France each year decreases while the frequency of this cancer increases. In addition, because the treatment considered hopeless is delayed, patients are seen at more advanced stages of disease, and too often, when the patient is in a terminal state, the radiotherapist is requested only to attempt to relieve pain or respiratory distress.

Most of the patients in a group of 57 with bronchogenic carcinoma considered inoperable (56% squamous cell carcinoma, 20% oat cell carcinoma, 5% adenocarcinoma, and 18% large cell anaplastic carcinoma) already had generalized disease when referred to our Department. Eleven patients were at a terminal stage and died during the treatment. Fifty-five percent had at the beginning or during the course of irradiation symptoms of one or more metastases (23% in the supraclavicular nodes, 26% in the liver, 7% in the central nervous system, and 15% in the bones). In general, the patients died as a result of metastasis (mostly in the liver) rather than from local growth at the primary site of the tumor. Nevertheless, irradiation in most cases has some effect, eg, relief of symptoms, or improvement of pulmonary collapse. Necropsy of one patient who died 2 months after irradiation revealed that the mediastinum and lungs were free of disease while important metastases had developed in the liver and brain.

All of the patients in this group died within 18 months with an average survival time of 5 months. These results are very depressing, but they are the results of the more common cases, not of selected cases. These results are not surprising if we compare them with some reported data that indicate the tendency of bronchogenic carcinoma to diffuse, not only in oat cell carcinoma, but also in epidermoid carcinoma.

Ratios of patients free of metastases at necropsy	Reported by—
0/361	Luomanen (1)
21/100	De Preux (2)
43/277	Israel [2]

[2] Israel, L. Personal communication.

[1] Department of Radiotherapy, American Hospital of Paris, Neuilly, France. Member of the Organisation Européenne de Recherche et de Traitement du Cancer (OERTC).

These results indicate that only 8.5% of patients would not benefit from systemic treatment.

So, we must make decisive progress or resign.

What pathways are available for progress?

A. *Increasing the dose to the primary tumor and mediastinum:* This is ineffective in controlling systemic disease; in addition, the incidence of serious and vital complications in the mediastinum is enhanced. Deeley (3) has shown that a tumor dose of 4000 rads produces worse results than a tumor dose of 3000 rads in patients with inoperable anaplastic carcinoma. Our experience with 300 mantle-field irradiations of the mediastina of patients with Hodgkin's disease suggests that the incidence of serious pericarditis is very high (26 cases); however, pericarditis never occurred in patients treated with less than 4500 rads.[3] In general, a dose to the mediastinum of 5000 rads in 5 weeks should not be exceeded.

B. Increasing the target volume of irradiation:

1. *Irradiation of supraclavicular areas.*—This is generally accepted for oat cell tumors, and probably could be used without serious objection for other carcinomas.

2. *Irradiation of the brain.*—This organ is frequently a site of metastasis, and is not accessible to most drugs because of the blood-brain barrier. Our experience with irradiation of the brain in 60 cases of acute leukemia (Acute Leukemia Group B protocol 71–11) indicates that a dose of 2400 rads in 2.5 weeks on the whole brain is well tolerated; in some cases, 3400 rads may be given. Therefore, a dose of 4000 rads in 4 weeks or 3000 rads in 2 weeks on the whole brain would appear to be safe.

3. *Irradiation of the liver* is not well tolerated when the dose is more than 2000 rads in 2 or 3 weeks.

These extrathoracic irradiations appear to be a new and interesting pathway of research justified by the diffusing character of the disease. However, they should be administered in conjunction with systemic treatment because they cannot deliver a curative dose and they cannot treat all the other possible sites of metastasis.

C. *Adjuvant chemotherapy:* Although most of the drugs have not given definitive results at this time, it seems that they are the best systemic treatment actually available.

D. *Immunotherapy:* The results obtained with this method need further confirmation, but the possibility of applying the method in any case without danger encourages its use on a large scale.

The protocol of the OERTC group (L. Israel, in charge) takes account of these new pathways of progress. The main target is to test the accuracy of systemic treatment (chemotherapy, immunotherapy, or both) in all cases after local surgical treatment and local radiotherapy.

OERTC Protocol

A. *Treatment of operable cases:*

Patients with epidermoid carcinoma in good local and general condition, 21 days after complete resection.

1. If nodes are negative, randomization in four arms:

a. No further treatment

b. Chemotherapy (cyclophosphamide, 5-fluorouracil, CCNU) [4]

c. Nonspecific immunotherapy (bacillus Calmette Guérin [BCG] vaccine)

d. Chemotherapy plus immunotherapy

2. If nodes are positive:

a. First randomization: with or without postoperative irradiation

b. Second randomization: with the same four arms described previously

[3] To be published at the International Congress of Radiology, Oct 1973.

[4] Cyclophosphamide: NSC-26271: CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan.

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8; 5-FU.

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

B. *Treatment of inoperable cases without evidence of metastasis:*

Radiotherapy in all cases, and subsequent randomization in the four arms described previously.

C. *Treatment of other cases:* chemotherapy.

In all cases of irradiation, the tissue dose is 5000 rads in 5 weeks on the mediastinum and supraclavicular areas. Further preliminary experience with irradiation of distant organs (brain, liver) is needed before routine use.

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A Clinical Trial of Methotrexate (NSC-740) and Radiation Therapy for Squamous Cell Carcinoma of the Lung [1]

R. D. Tucker, R. Sealy, C. van Wyk, C. L. Soskolne, and P. L. M. le Roux [2,3]

This paper reports a prospective clinical trial on locally inoperable squamous cell carcinoma of the lung to determine whether the added use of methotrexate at the time of radiation therapy improved the survival rate of the patients. The study began in 1968. The patients were randomly assigned to a schedule of either radiation therapy alone or radiation therapy with methotrexate. Those patients accepted into the trial had inoperable disease that was clinically and radiologically confined to the thorax and all had a histologic diagnosis of squamous cell carcinoma of the lung. Patients who had palpable supraclavicular nodes were accepted. The presence of emphysema or chronic bronchitis did not exclude a patient from the study; however, those with superior mediastinal syndrome, malignant pericarditis, distant metastases, or those who had had previous treatment were not accepted.

At the beginning of the study, each patient received 250 mg of tetracycline qid orally for 5 days plus supportive symptomatic therapy. No steroid therapy was given during the course of the study.

Treatment with radiation consisted of cobalt therapy to the anterior and posterior opposing fields. The whole of the clinical and radiologic tumor volume was included in the treatment area which in no case exceeded 180 cm². A midplane dose of 3000 rads in 12 days was given in 10 fractions. Those patients treated with methotrexate received exactly the same radiation therapy, but in addition received a daily dose of 5 mg of methotrexate given by rapid intravenous (iv) injection immediately before each radiation treatment. The addition of methotrexate at this dose level and its use in this way did not produce significant side effects; in particular stomatitis, diarrhea, leukopenia, and thrombocytopenia were not noted.

In this trial, eight patients received radiation therapy alone, and 12 patients received radiation therapy plus methotrexate. The survival rates of the two groups of patients are shown in figure 1. Notice that in both groups the curves are roughly those of a straight line.

[1] Methotrexate: CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-.

[2] Radiotherapy Department, Groote Schuur Hospital, and the University of Cape Town, South Africa.

[3] The authors would like to thank Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for his permission to publish the cases in this report.

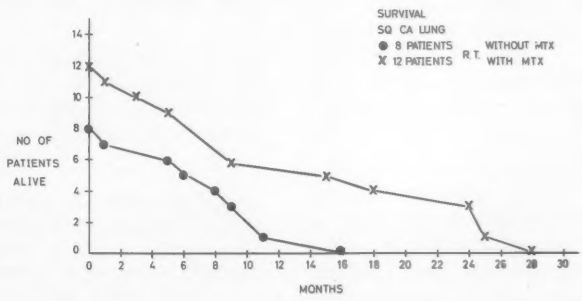

FIGURE 1.—Survival rates of patients treated with radiation therapy (RT) alone and radiation therapy plus methotrexate (MTX).

All of the patients treated with radiation therapy alone were dead at 16 months, whereas three patients in the methotrexate group survived beyond this time (24, 25, and 28 months, respectively). The difference in survival rate between the two groups of patients is judged to be significant at the 10% level by the use of the "Student's t" test.

Perhaps unfortunately this study was terminated early to allow for participation in a joint study with other centers. It is considered, nevertheless, that there is a place for the use of methotrexate combined with radiation therapy in the treatment of squamous cell bronchogenic carcinoma in the manner described, and that further attempts should be made to confirm the preliminary results reported here.

A Clinical Trial of Cyclophosphamide (NSC-26271) and Radiation Therapy for Oat Cell Carcinoma of the Lung [1]

R. D. Tucker, R. Sealy, C. van Wyk, P. L. M. le Roux, and C. L. Soskolne [2]

SUMMARY

A clinical trial in oat cell carcinoma of the lung suggests that large doses of cyclophosphamide allow a longer survival time than irradiation of the chest. This is possibly due to the influence of cyclophosphamide on the metastatic manifestations of the disease.

[Cancer Chemother Rep Part 3, vol 4:159–160, 1973]

The use of cyclophosphamide and radiation therapy in the treatment of small cell carcinoma of the lung was studied in a prospective clinical trial to compare the survival rates of patients treated with each of the two methods. The study began in 1968. The patients were randomly assigned to a schedule of either radiation therapy alone or cyclophosphamide alone.

Those patients accepted for the study had diseases which were clinically confined to the thorax and all had a histologic diagnosis of small round cell carcinoma. Patients with palpable supraclavicular nodes were accepted. The presence of emphysema or chronic bronchitis did not exclude patients from the study; however, those with superior mediastinal syndrome, malignant pericarditis, distant metastases, or those who had had previous treatment were not accepted.

At the beginning of the trial, each of the patients received 250 mg of tetracycline qid orally for 5 days plus supportive symptomatic therapy. No steroid therapy was given during the course of the study.

Treatment with cyclophosphamide consisted of two doses of 50 mg/kg of body weight. The first dose was given when the patient was entered into the study and the second dose was given 5 week later. The method of radiation therapy used was the "shrinking field technique." The general approach to this method of treatment is shown in figure 1. It will be seen that initially a large volume is irradiated, usually the whole mediastinum and the involved hemithorax, but as the tumor regresses under the influence of radiation therapy the volumes treated are progressively reduced in size. In this study the mediastinum and involved hemithorax were treated through two opposing fields at a central dose of 1500 rads in 10 fractions in 12 days. Following this, the patient rested for 1–2 weeks. The remaining tumor mass, as judged by clinical examination or radiographs of the chest, was treated with an additional 2250 rads in 10 fractions in 12 days. Again, two opposing fields were used. The treatment modality was 250 kilovolts, 3.5 mm^3 half-value layer X-rays.

Eleven patients were treated with the shrinking field technique and 14 patients were treated with cyclophosphamide. Two of the latter group, however, were lost to followup and were excluded from the report of the study.

The survival rates of the patients are shown in figure 2. With the shrinking field technique all patients were dead at 8 months and the

[1] Cyclophosphamide: CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

[2] Radiotherapy Department, Groote Schuur Hospital, and the University of Cape Town, South Africa.

[3] The authors would like to thank Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for his permission to publish the cases in this report.

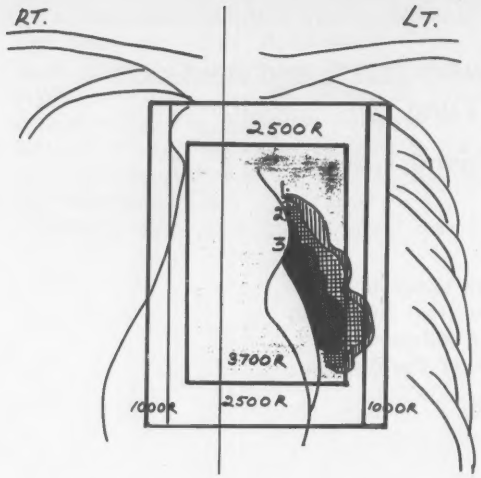

FIGURE 1.—General approach to the shrinking field technique of radiotherapy.

survival curve has perhaps a sinusoidal shape. In the cyclophosphamide group, a marked early mortality is also noted but four patients survived for 10 months or more and one patient with metastases has survived for 21 months. This would suggest that the use of cyclophosphamide in this fashion may be associated with an improved survival rate for patients with this disease. The results reported here are considered statistically significant at the 5% level as judged by the "Student's t" test.

It could be considered that the use of radiation therapy produces improved local control of the disease whereas the use of cyclophosphamide produces improved metastatic control of the disease. It is, therefore, of interest to consider the sites of failure in the two groups. These are shown in table 1. With the radiation treatment, five patients had predominantly local disease at the end of their lives and six had gross metastases. On the other hand, where cyclophosphamide was used, eight patients had predominantly local disease at the end of their lives and in only four patients were metastases the major problem. This would tend to support the contention that local manifestations of the disease are controlled somewhat better by radiotherapy in moderate doses and that the use of cyclophosphamide early in the course of the patient's treatment may be associated with the delay of the gross manifestations of metastatic spread.

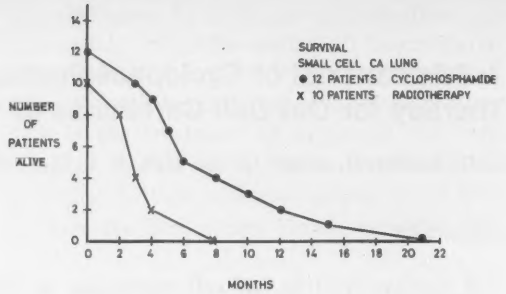

FIGURE 2.—Survival rates of patients treated with radiotherapy alone and with cyclophosphamide alone.

TABLE 1.—Clinical and radiographic sites of failure with two types of therapy

Type of therapy	Site of failure		Total No. of patients
	Local	Metastatic	
Radiation	5	6	11
Cyclophosphamide	8	4	12

Cyclophosphamide (NSC-26271) as Adjuvant to Radiotherapy in the Treatment of Unresectable Bronchogenic Carcinoma [1]

Herman Høst [2]

SUMMARY

One hundred and forty-nine patients with unresectable bronchogenic carcinoma were assigned at random to treatment with either radiotherapy alone or radiotherapy with adjuvant cyclophosphamide (administered intravenously concurrently with the radiation). The survival of patients with epidermoid cell carcinoma treated with the combination was not increased compared with that of patients with epidermoid cell carcinoma treated with radiation alone. However, the results may indicate that cyclophosphamide as adjuvant to radiation reduced the mortality of patients with undifferentiated small cell carcinoma during the first months.

[Cancer Chemother Rep Part 3, vol 4:161–164, 1973]

Radiotherapy in combination with cyclophosphamide may slightly improve survival in patients with unresectable bronchogenic carcinoma. In one study, radiotherapy alone prolonged life by approximately 15% as compared with untreated controls (1); in another study, intravenous (iv) administration of cyclophosphamide alone increased the survival rate by approximately 20% (2). The latter effect was most marked in patients with undifferentiated small cell carcinoma. Gollin et al (3), however, were not able to demonstrate any advantage in using radiotherapy and adjuvant cyclophosphamide compared with radiotherapy alone in a small series of patients with bronchogenic carcinomas of various histologic types.

In some pilot studies, we had encouraging results in patients with inoperable bronchogenic carcinoma treated by radiation and adjuvant cyclophosphamide. In spite of the results obtained by Gollin et al (3), we found it worthwhile to study the effect of this combined treatment in a prospective study in which the patients were assigned at random to treatment with either radiotherapy alone or radiotherapy with adjuvant cyclophosphamide. Distinction has been made between epidermoid cell carcinoma and undifferentiated small cell carcinoma.

PATIENTS AND METHODS

Patients with nonresectable bronchogenic carcinoma admitted to the hospital from August 1968 to December 1971 were evaluated with regard to possible inclusion in the trial. The clinical evaluation included a detailed history and a physical examination with special attention to symptoms and signs indicative of metastatic involvement. Laboratory examinations consisted of a complete peripheral blood cell count; platelet count; determination of values for serum urea, serum creatinine, serum alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH); and thymol turbidity test. If liver function test results were abnormal or

[1] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl) amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan; Sendoxan; Endoxan.

[2] The Norwegian Radium Hospital, Oslo, Norway.

hepatomegaly was present, a liver scan (with 2.0 millicuries of technetium 99 sulphur colloid) was performed. The routine radiographic evaluation included only posteroanterior and lateral chest films; skeletal survey was performed when symptoms or signs of bone metastases were present.

Patients of any age and either sex were eligible for the trial provided that:

(*a*) A diagnosis of either epidermoid cell carcinoma or undifferentiated small cell carcinoma (oat cell) had been established by either biopsy of the primary tumor or the regional lymph nodes, or exfoliative cytology of sputum or bronchoscopy material. The histologic typing was performed according to WHO Classification (4).

(*b*) No clinical, laboratory, or radiographic evidence was found of tumor spread beyond the lymph nodes in mediastinal, hilar, or supraclavicular areas.

(*c*) The tumor was considered technically inoperable because there was local infiltration and/or regional lymph node involvement or because the patient was not regarded suitable for resection of the growth because of impaired cardiac/pulmonary function.

(*d*) The patient was considered fit enough for radiotherapy and adjuvant cyclophosphamide therapy.

Assignment to treatment group was made by reference to lists based on random numbers. The assignment was to treatment with either radiotherapy alone or radiotherapy with adjuvant cyclophosphamide.

Followup examinations were performed at 2-month intervals after radiotherapy was completed, or more frequently if indicated. The only parameter for evaluation of treatment effect has been survival which was tabulated from the first day of treatment.

The *irradiation* was carried out with one of the following apparatus: a 31-megavolt betatron (Brown Boweri Askeplitron), a cobalt 60 machine (Siemens Gammatron 3), or an 8-megavolt linear accelerator (Vickers Series 3). One anterior field was used for patients treated with the betatron, whereas opposed anterior and posterior fields were used for patients treated with the ^{60}Co machine or the linear accelerator. The fields included all demonstrable ipsilateral pulmonary involvement and the mediastinum to the suprasternal notch. The ipsilateral neck region was included when there were palpable masses, or when the pulmonary lesion was present in the apical part of the lung. The tumor dose was 4000 rads for the undifferentiated small cell carcinomas and 5000 rads for the epidermoid cell carcinomas with a daily tumor dose of 160–200 rads. The overall treatment time was 4–5 and 5–6 weeks, respectively.

Cyclophosphamide was administered iv concurrently with radiation in daily doses of 400 mg up to a total dose of 40 mg/kg of body weight. About 2 weeks after the completion of the iv course, orally administered maintenance therapy with cyclophosphamide was started with a daily dose of 100 mg; this was to be given for the rest of the patient's life. However, for some of the patients assigned to treatment with the combination of radiation and cyclophosphamide, maintenance therapy had to be discontinued because of nausea and vomiting.

Secondary treatment with radiotherapy or cytotoxic chemotherapy was permitted when it was considered that such treatment would make the illness less distressing or would influence survival, but it was hoped that secondary treatment would not be applied as a general rule.

RESULTS

One hundred and forty-nine patients (74 with epidermoid cell carcinoma and 75 with undifferentiated small cell carcinoma) were suitable for inclusion in the trial. There were three women and 71 men in the group with epidermoid cell carcinoma; the median age was 67 years (range, 32–79 years). There were four women and 71 men in the group with undifferentiated small cell carcinoma; the median age was 63 years (range, 42–74 years).

The crude survival rates for patients with epidermoid cell carcinoma are shown in figure 1. Fifty percent of the patients treated

with radiation alone were alive at 8.5 months and 20% were alive at 24 months, whereas 50% of the patients treated with the combination were alive at 10.5 months and 20% were alive at 16 months.

The results for the undifferentiated small cell (oat cell) carcinomas are shown in figure 2. The pattern of the curves indicates a higher rate of mortality during the first months following treatment in the patients who had radiotherapy alone, whereas the curves are almost identical later. Fifty percent of the patients treated with radiotherapy alone were alive at 5.5 months; 50% of the patients treated with radiation and adjuvant cyclophosphamide were alive at 8.5 months.

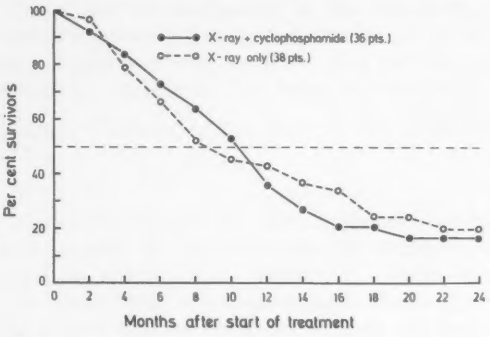

FIGURE 1.—Crude survival rates of patients with epidermoid cell carcinoma of the lung treated by irradiation alone or by irradiation with adjuvant cyclophosphamide.

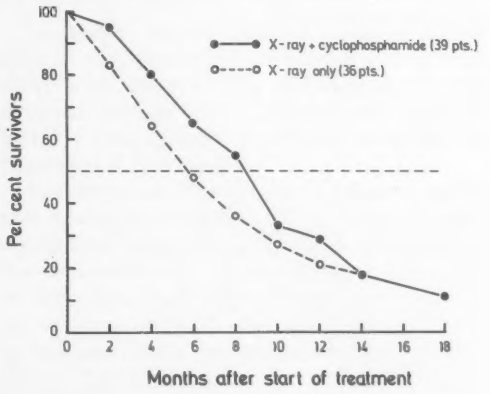

FIGURE 2.—Crude survival rates of patients with undifferentiated small cell (oat cell) carcinoma of the lung treated by irradiation alone or by irradiation with adjuvant cyclophosphamide.

TOXICITY

Both iv and oral administration of cyclophosphamide caused troublesome symptoms in many patients. During the iv course, nausea and vomiting occurred in almost all patients, but none had symptoms severe enough to require discontinuation of treatment. However, in some of the patients receiving oral maintenance treatment, these symptoms were severe enough to require discontinuation of treatment. Transient alopecia was observed in about half of the patients.

Leukopenia occurred frequently, and white blood cell counts less than 2000/mm³ were noted in 28% of the patients who received adjuvant cyclophosphamide therapy; thrombocytopenia was not a problem. The hematologic toxic effects required no special measures and did not hinder uninterrupted radiation therapy.

COMMENT

Radiotherapy with adjuvant cyclophosphamide did not seem to be superior to radiotherapy alone in the treatment of epidermoid cell carcinoma. However, in patients with undifferentiated small cell carcinoma, our results indicate some advantages in this combined therapy during the first months; this may possibly be attributed to the parenteral administration of cyclophosphamide. Green et al (2) found no effect on survival in patients with bronchogenic carcinoma treated orally with cyclophosphamide. In future studies, improved effect may perhaps be obtained by giving cyclophosphamide iv in intermittent courses as a single agent or, even better, in combination with other drugs (5).

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Alternative Approaches to Radiotherapy Alone and Radiotherapy as a Part of a Combined Therapeutic Approach for Lung Cancer [1]

Lars R. Holsti [2]

SUMMARY

A short review is given on experiences with split-course radiotherapy administered alone and in combination with atmospheric oxygen and chemotherapy in the treatment of lung cancer. The author's present practice of treatment is described. Previous studies on autopsy material indicate that the dosage required to destroy bronchial carcinoma lies between 4800 and 6000 rads.

[Cancer Chemother Rep Part 3, vol 4:165–169, 1973]

Carcinoma of the bronchus is the most common cancer in Finland and the number of cases is continuously increasing. There are now about 2000 new cases a year. Finland has the second highest incidence of lung cancer in the world after Great Britain.

Lung cancer has been treated by radiotherapy at our Clinic since the late 1930's (1).

SPLIT-COURSE RADIOTHERAPY ALONE

In 1964 a clinical trial was started in Helsinki to compare the results of split-course treatment with those of the ordinary daily fractionated method (2). Lung cancer cases for which 4-year survival results are available are presented in this section.

The material is classified by clinical spread and histologic distribution in table 1 which shows that there are no striking differences in the composition of the randomized therapeutic groups. The incidence of squamous cell carcinoma was 46% in the split-course therapy group and 43% in the continuous therapy group. The group labeled "other carcinomas" included patients with unclassified carcinoma or adenocarcinoma, as well as patients with carcinoma that was verified cytologically only.

The survival rates are compared in figure 1. The survival curves run nearly parallel throughout the observation period.

The survival rate according to histologic type is shown in table 2. The difference (in favor of the split-course method) was clearest in patients with squamous cell carcinoma, whereas the difference was minimal in patients with anaplastic, small cell, or other types of carcinoma.

Split-course therapy is easier on the patient and results in considerably lower radiation morbidity. Consequently, the reaction of the lung tissue to radiation is milder after split-course therapy and occurs 2 months later than after continuous radiotherapy (3). The dose is increased by 10% to compensate for the rest interval.

PRESENT PRACTICE AND TREATMENT SCHEDULES

The trial of split-course radiotherapy was stopped at the end of 1967 and a new trial in which the split-course regimen is compared with a modified split-course regimen has been started. In the modified split-course regimen, the first part of the dose is fractionated twice

[1] Supported by a research grant from the Sigrid Juselius Foundation.

[2] Chief, Radiotherapy Clinic, University Central Hospital, Helsinki, Finland.

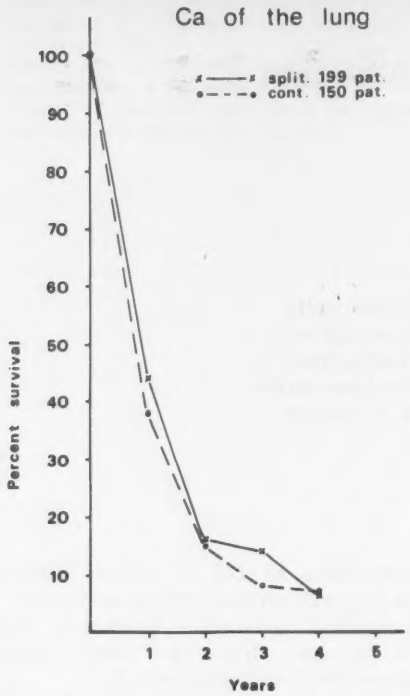

FIGURE 1.—Survival curves for patients treated with radiotherapy alone.

TABLE 1.—Clinical spread and histologic type of carcinoma of the lung in patients treated with split-course or continuous therapy

Disease characteristics	No. of patients receiving— Split-course therapy	Continuous therapy
Clinical spread		
No metastases	39 (20%)	29 (19%)
Intrathoracic spread	160 (80%)	121 (81%)
Total	199	150
Type of tumor		
Squamous cell carcinoma	92 (46%)	64 (43%)
Anaplastic and small cell carcinoma	66 (33%)	56 (37%)
Other carcinomas*	41 (21%)	30 (20%)
Total	199	150

*Unclassified carcinoma, adenocarcinoma, or carcinoma that was verified cytologically only.

TABLE 2.—Results of treatment of patients with carcinoma of the lung in relation to histologic type

Type of tumor	Split-course therapy: No. of patients treated	No. of patients surviving— 1 yr	2 yrs	3 yrs	Continuous therapy: No. of patients treated	No. of patients surviving— 1 yr	2 yrs	3 yrs
Squamous cell	92	52 (56%)	21 (23%)	9/58 (15%)	64	31 (48%)	13 (20%)	6/53 (11%)
Anaplastic + microcell	66	20 (30%)	7 (11%)	2/42 (5%)	56	15 (27%)	4 (7%)	1/42 (2%)
Other*	41	16 (39%)	5 (12%)	5/37 (13%)	30	11 (36%)	6 (20%)	3/26 (11%)
Total	199				150			

*Unclassified carcinoma, adenocarcinoma, or carcinoma that was verified cytologically only.

weekly and the second part is fractionated daily. This new trial is handled by my colleague, Dr. Torsti.

Radical radiotherapy can be given to patients in whom the spread of the tumor does not exceed T3 N1 M0 (according to the TNM classification system recommended by the International Union Against Cancer [UICC] [4]) if the patient is in good condition and has an erythrocyte sedimentation rate (ESR) of less than 70. The patient must have no pyrexia or anemia. Radical radiotherapy is usually too much for patients more than 70 years old. Pulmonary function must exceed 50% of the normal function. Compensated cardiac insufficiency is not a contraindication.

The *treatment volume* covers the primary tumor and the mediastinum. The therapy is usually given with betatron roentgen rays (33-megavolt photons; an 8-megavolt linear accelerator has been ordered).

Fractionation is either a normal split-course

$$\frac{\text{2750 rads/12 fractions (F)}}{\text{2½ weeks}} \quad \text{3 weeks} \quad \frac{\text{2750 rads/12 F}}{\text{2½ weeks}} = \frac{\text{5500 rads/24 F}}{\text{8 weeks}},$$

or a modified split-course therapy (randomized clinical trial)

$$\frac{\text{2250 rads/5 F}}{\text{2½ weeks}} \quad \text{3 weeks} \quad \frac{\text{2750 rads/12 F}}{\text{2½ weeks}} = \frac{\text{5000 rads/17 F}}{\text{8 weeks}}$$

Antibiotic prophylaxis is used during irradiation and during the interval between treatments.

Palliative radiotherapy is given to patients with a tumor spread of more than T3 N1 M0 or to those who are in poor general condition or have ESRs exceeding 70. Respiratory function must be more than 50% of the normal function.

The treatment volume covers the primary tumor and the mediastinum, and the treatment is usually with 33-megavolt photons.

Fractionation is 5 plus 5 fractions, given twice weekly, with an interval of 3 weeks halfway through the course. The total tumor dose is 4500 rads in 8 weeks.

Metastases detected in the clavicular fossa or in other locations may be treated on the intermediate days if the patient's general condition is good enough. This method gives a sufficient radical dose to the treatment area. If the patient is considered unable to tolerate this, a palliative dose of 5 × 400 rads to the tumor is given on consecutive days. This includes patients with pulmonary function less than 50% of the normal. To date, no fibrosis has developed with this dosage.

In cases of superior vena caval obstruction (SVCO), daily fractions of 200–220 rads are given to the tumor from an anterior field up to a total of 2500–3000 rads; this is followed by an interval and further therapy as the situation requires.

In special cases, palliative therapy has been given with X-ray sieve therapy.

Primary chemotherapy may be considered for patients with anaplastic or small cell carcinoma. Cyclophosphamide[3] has been given intravenously (iv) in short, intensive courses at a dose of 40 mg/kg divided over 4 days. This chemotherapy should consist of not less than three courses at 4-week intervals.

An alternative is a course of combination chemotherapy with cyclophosphamide and vincristine.[4] The cyclophosphamide dosage is as stated previously supplemented with 1 mg of vincristine given iv on the first and fourth days of the course. This has also been repeated at least three times. In selected cases, radiotherapy may be given after the first course of chemotherapy.

If the anaplastic or small cell tumor has metastasized during radical radiotherapy, treatment is continued with chemotherapeutic agents according to the described schedule. In cases of highly differentiated carcinoma, the metastases are treated with radiation after completion of the radical therapy.

COMBINED SPLIT-COURSE THERAPY

Chemotherapy

The results obtained with the combination of single-agent chemotherapy and split-course radiotherapy have not been convincing.

In Gollin's series (5) the survival time was not increased. These results contrast with those obtained in a single-course series (6). Cook et al (7) concluded that mechlorethamine[5] does not increase the life expectancy in patients with lung cancer irradiated by the split-dose technique.

In a randomized study (8) we compared the results of radiation plus 5-fluorouracil[6] therapy (both administered by the split-course technique) with the results obtained with split-course radiation alone (table 2). The

[3] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

[4] Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1).

[5] Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride; HN2; nitrogen mustard.

[6] 5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8; 5-FU.

distribution of the cases by histologic type is shown in table 3; it appears that there were no significant differences in this respect. The survival data are shown in figure 2. The 1- and 2-year survival rates are approximately the same in the two groups, but at 3 years or more, the results for the combined treatment group are more favorable. Two patients, both belonging to this group, survived 5 years. One had a cytologically verified malignant tumor; the other, still living after 7 years, had anaplastic carcinoma. In the group given radiotherapy alone, the longest survival time was 2 years and 9 months. The mean survival time of the patients who died was 13.5 months in the group treated with radiotherapy alone and 13.4 months in the group treated with radiotherapy plus 5-FU.

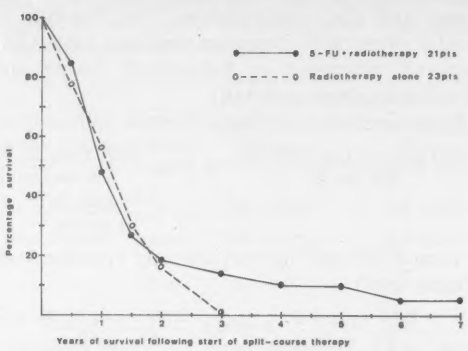

FIGURE 2.—Survival curves for patients treated with combined split-course therapy.

TABLE 3.—Distribution of cases of carcinoma of the lung by histologic type

Histologic type	Split-course radiotherapy	Split-course radiotherapy plus 5-FU
Squamous cell carcinoma	11	7
Unclassified carcinoma	3	4
Anaplastic carcinoma	5	6
Small cell carcinoma	2	1
Cytology only	2	3
Total	23	21

Oxygen

The administration of atmospheric oxygen during split-course radiotherapy has not increased the survival according to a nonrandomized study (9) in which 30 patients breathed oxygen during radiotherapy and 73 patients treated by the corresponding fractionation schedule breathed air. Similar experiences have been reported by others (10).

AUTOPSY OBSERVATIONS

A few years ago, we conducted a study to establish from autopsy material whether megavoltage therapy in the conventional dosage is capable of destroying primary lung carcinoma (11). The material was obtained from 67 patients with histologically verified inoperable carcinoma of the lung treated by megavoltage therapy during the period 1963–1967 and examined by autopsy 2 months to 4 years and 1 month (average, 9 months) later. Because the time from treatment to autopsy varied greatly, it was not possible to distinguish between residual tumors and recurrences.

The findings were divided into four groups according to the type of primary growth at autopsy: Group 1, no carcinomatous tissue evident; Group 2, no definite malignancy observed macroscopically, but fibrosis with obvious islets of carcinoma cells observed microscopically; Group 3, necrotic areas with malignant infiltration; and Group 4, viable malignant tissue in the treated area.

The correlation between autopsy findings and radiation dose is shown in table 4. It appears that, under favorable conditions, it is possible to destroy the primary focus of pulmonary carcinoma with a dose of 4800–6000 rads.

The carcinoma actually disappeared microscopically in 18 (30%) of the patients who had received the full planned course of at least 4800 rads. There had been no complicating factors in these patients. Fourteen (78%) of these patients had been treated by the split-course technique. This suggests that the method has definite advantages. Bearing in mind

TABLE 4.—Correlation between autopsy findings and radiation dose

Group	Autopsy findings	No. of patients treated with— 4000 rads	5000 rads	6000 rads	Total No. of patients
1	No carcinoma	8	8	2	18
2	Fibrosis	3	7	4	14
3	Necrosis	4	2	—	6
4	Viable carcinoma	6	11	5	22
	Total	21	28	11	60

that there was no true random selection of cases for split-course or continuous therapy in this series, we may note that the primary tumor disappeared completely in 37% of the patients treated by the former method and in only 14% of those treated by the latter method.

All patients who had a complete loss of malignant tissue had received more than 4800 rads. Fourteen patients (23%) had islets of carcinoma cells in the fibrotic areas. Recurrence might well have arisen from such residual foci. In those groups in which viable carcinomatous tissue or necrotic areas with islets of malignancy were found at autopsy in the treated area, over half the patients (67% in Group 3, 50% in Group 4) had had complications during therapy. This had prevented the realization of the radiotherapeutic plan and, thus, impaired the end results.

In only a few rare cases in which the therapeutic program had been completed without noteworthy complicating factors (at a dose of 4000–6000 rads) was viable carcinomatous tissue demonstrated at autopsy. Only the individual radiosensitivity of each tumor can properly account for this; anoxic cells are an important factor in this radiosensitivity. It was not possible to determine the critical dose for different histologic types of carcinoma. Material for more definitive conclusions is being collected.

Theoretical studies on cell damage in this autopsy material using a single-hit, multitarget model indicate that there is a boundary value below which the cell survival fraction must go before the destruction of the tumor is achieved (11).

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Combination Chemotherapy and Radiation Therapy for Small Cell Carcinoma of the Lung [1]

L. Herbert Maurer, Marchant Tulloh, Robert T. Eagan, R. Jackson Forcier, and Reginald House [2,3]

Small cell carcinoma of the lung becomes a disseminated disease early in its course. The failure of surgical and radiation therapy to alter, to any significant extent, the survival of patients with this disease has been discussed, and less than 1% of the patients treated in this manner are alive at 5 years. Because of its rapid proliferation, large growth fraction, and early metastatic potential, it is a tumor in which systemic chemotherapy could ideally be employed provided effective agents can be found. Further, radiation therapy provides the potential for eradication of the bulk of the tumor by sterilization of the primary focus of disease.

Two years ago, we began to study possible methods of using combination chemotherapy and radiation therapy in the treatment of small cell carcinoma of the lung. Our phase II study has evolved rapidly and has employed several drugs, doses, and schedules with radiation therapy. The preliminary results have led to the design of a combination chemotherapy and radiation therapy protocol which has been activated by the Acute Leukemia Cooperative Study Group B (ALGB). The protocol has been designed for a homogeneous group of patients with small cell carcinoma of the lung.

The purpose of this phase II study was threefold. The major purpose was to find a combination of active agents which could be used in a cyclic fashion in the treatment of disseminated small cell carcinoma. It became apparent early in the study that radiation therapy would have to play an integral part in the overall therapy in order to control the primary lung tumor.

A benefit of the chemotherapy study design was the ability to determine the individual activity of procarbazine and methotrexate in this carcinoma after the regressions produced by the combination of cyclophosphamide and vincristine had occurred.[4] This is important because published information on single drugs is quite scanty when applied to cell type. As will be seen from the data, the combination of cyclophosphamide and vincristine may be substantially more active than either agent alone in this disease.

The second purpose of this study was to determine the frequency of bone marrow metastases at the time of the initial diagnosis.

The third purpose of this study was to determine the frequency of clinically apparent hormonal and neurologic syndromes produced by this tumor.

MATERIALS AND METHODS

Thirty-six patients who have had histologic or cytologic documentation of small cell carcinoma of the lung have been studied over the past 22 months. Only four patients were diagnosed by sputum cytology, but all had evidence

[1] Supported in part by grant CA-04326 from the National Cancer Institute, National Institutes of Health, Public Health Service.

[2] Sections of Hematology-Oncology and Radiation Therapy, Department of Medicine, and the Department of Pathology, Dartmouth-Hitchcock Medical Center, Hanover, NH.

[3] *Reprint requests to:* L. Herbert Maurer, MD, Section of Hematology-Oncology, Department of Medicine, Dartmouth-Hitchcock Medical Center, Hanover, NH 03755.

[4] Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride.

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1).

of a pulmonary mass lesion. Thirty patients have been placed on one of the three protocols. Two of these patients died of extensive disease during the first 2 weeks after therapy was begun. It is too early to evaluate three of the patients and two have not responded to chemotherapy.

Seventy-five percent of the patients had extensive disease in both lungs or extrathoracic dissemination. Responses were classified as complete when all objective evidence of disease had disappeared including hormonal or neurologic syndromes. Bone marrow examinations were not, however, performed at the time of a complete response. A partial response was defined as a greater than 50% reduction in the size of all measurable masses.

The following regimens have been used in a cyclic fashion (fig 1). On Day 1 of the first course, cyclophosphamide and vincristine were given at full dose in all three schedules regardless of the hematologic parameters. In schedule I procarbazine was employed at full dose even if the white blood cell count was significantly depressed by the preceding course of cyclophosphamide. Procarbazine was selected because of a delayed onset of hematologic toxic effects and because of its reported value by Samuels et al (2) in producing objective responses in seven of nine patients. During the subsequent cycles the cyclophosphamide dose level was adjusted downward according to prescribed hematologic parameters. Vincristine was also decreased according to a set schedule for dose level adjustment. In schedule II methotrexate was given on Days 21 and 28 of each 5-week cycle. In schedule III methotrexate was given on Day 21 of each 4-week cycle. Dose level modifications for methotrexate were also prescribed.

Radiation therapy was given prior to or concomitantly with cycle No. 1 in schedule II, employing 4000–5000 rads over a 4–5-week period. Unfortunately, when this course was administered concomitantly with chemotherapy there were significant breaks in both radiation therapy and chemotherapy due to hematologic toxic effects.

Subsequently, an alternate but biologically equivalent radiation therapy regimen was employed using 3200 rads to the primary lung tu-

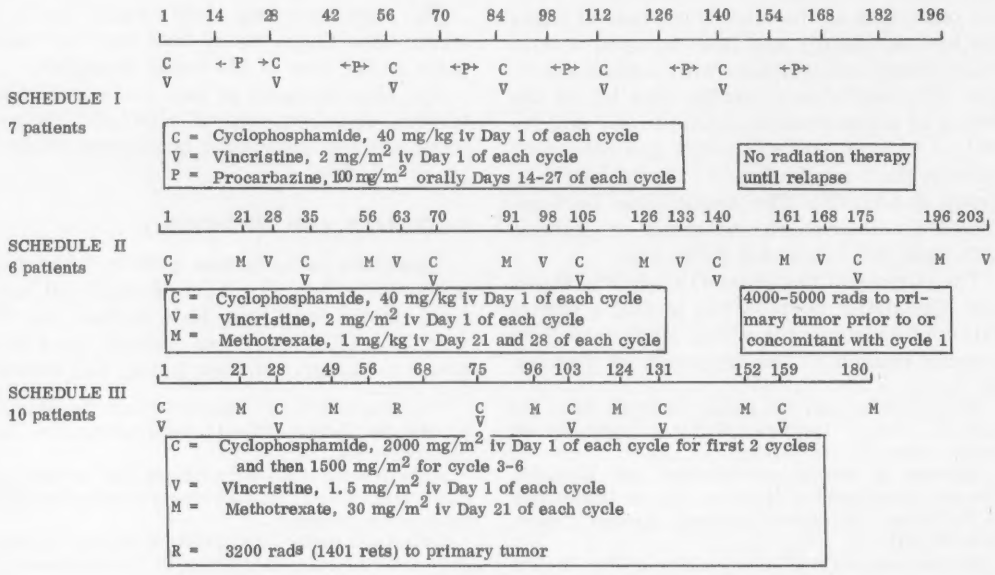
SCHEDULE I
7 patients
C = Cyclophosphamide, 40 mg/kg iv Day 1 of each cycle
V = Vincristine, 2 mg/m2 iv Day 1 of each cycle
P = Procarbazine, 100 mg/m2 orally Days 14-27 of each cycle
No radiation therapy until relapse
SCHEDULE II
6 patients
C = Cyclophosphamide, 40 mg/kg iv Day 1 of each cycle
V = Vincristine, 2 mg/m2 iv Day 1 of each cycle
M = Methotrexate, 1 mg/kg iv Day 21 and 28 of each cycle
4000-5000 rads to primary tumor prior to or concomitant with cycle 1
SCHEDULE III
10 patients
C = Cyclophosphamide, 2000 mg/m2 iv Day 1 of each cycle for first 2 cycles and then 1500 mg/m2 for cycle 3-6
V = Vincristine, 1.5 mg/m2 iv Day 1 of each cycle
M = Methotrexate, 30 mg/m2 iv Day 21 of each cycle
R = 3200 rads (1401 rets) to primary tumor

FIGURE 1.—Regimens for the treatment of small cell carcinoma of the lung.

mor in ten doses over a period of 12 days. This regimen was administered after the second course of chemotherapy as represented in schedule III and represents a nominal standard dose (NSD) of 1401 rad equivalent therapy (rets). This lower dose limited the break in chemotherapy, which kept the systemic disease under control, but did not sacrifice the therapeutic effects of radiation.

RESULTS AND DISCUSSION

Twenty-five patients have completed at least one full cycle of chemotherapy and could be analyzed for survival or response data. However, because of the simultaneous use of chemotherapy and radiation therapy in two patients with localized disease, it is impossible to evaluate their response to drugs except in terms of survival. Twenty-three patients, therefore, have had evaluable responses to cyclophosphamide and vincristine or to cyclophosphamide alone as seen in table 1. Two patients were treated with cyclophosphamide alone and only one responded. The other patient who had the myasthenic syndrome subsequently responded to the combination of cyclophosphamide and vincristine. Ninety percent of the patients who received the combination of cyclophosphamide and vincristine had objective responses with the initial dose that ranged from objective improvement to complete remission.

Because of the dramatic regressions produced by cyclophosphamide and vincristine, it was easy to see the subsequent response to the third drug. The response to procarbazine was somewhat discouraging in the method and dose level used. Only one of seven patients showed objective regression of disease during the 2-week course. More important was the fact that objective evidence of progression occurred during this 2-week period in five patients.

TABLE 1.—Objective responses to chemotherapy

Drug	No. of responses/ total No. of patients	Responses (%)
Cyclophosphamide alone	1/2	50
Cyclophosphamide + vincristine	20/22	90
Procarbazine alone	1/7	14
Procarbazine alone (objective response + no progression)	2/7	28
Methotrexate alone	7/20	35
Methotrexate alone (objective response + no progression)	16/20	80

A subsequent switch to methotrexate in two of the patients who had progressed on procarbazine showed that their disease either remained stable or receded during the time that methotrexate was administered. In schedules II and III methotrexate was used as the third drug, given initially on Days 21 and 28 and ultimately on Day 21 only. The reason for limiting it to one dose was that significant leukopenia occurred after the second dose of methotrexate, which resulted in the modification of the subsequent cyclophosphamide dose. The response rate to methotrexate alone was an encouraging 35%. No progression of disease was seen in an additional 45% of the patients, which suggests that methotrexate is active, at least when compared with procarbazine.

Radiation therapy was active in all dose schedules and was capable of removing the bulk of the primary tumor which often caused the most significant symptoms. When radiation therapy was administered concomitantly with chemotherapy, however, there were significant breaks in both the chemotherapy and the radiation therapy regimens. The alternate shorter course of radiation therapy proved to be as active as the longer course. By placing this radiation course after the first two cycles of chemotherapy, several patients who were initially rejected by the radiation therapists because of disseminated disease have become eligible for radiation therapy. In addition, the bulk of the primary tumor mass is smaller, which may improve the capability for radiotherapeutic sterilization. Local and systemic toxicity was no greater from radiotherapy administered in this fashion.

In the past, our experience with small cell carcinoma has been similar to that of other researchers, with a median survival rate of 3 months for the 47 patients in our tumor registry (table 2). There were minimal differences between patients with local, regional, or disseminated disease, which undoubtedly reflects an

TABLE 2.—Survival in previously studied patients

Stage of disease	No. of patients	Median survival (mos)
Local	1	7
Regional	19	5
Metastatic	27	2
Total	47	3
Treatment with radiation therapy	24	5.5

inadequate knowledge of the staging of this disease.

We have attempted to project the results of our phase II study to a life-table analysis to see what benefits this combination may provide in terms of improvement in survival rates. While the confidence limits overlap, a definite trend can be seen in figure 2. In the lower curve is the survival rate for the patients treated with procarbazine. In the upper curve are all 16 patients who have responded after at least one cycle of chemotherapy that included methotrexate. Of more importance is a curve (not shown) of the ten patients on schedule III in which the survival curve at the present time is a straight line at 100% survival after 11 months of therapy; the number of patients at each point, however, is small. In addition, there is a significant difference in the complete remission status achieved by the three groups that were studied (table 3).

We have confirmed the observation of Hansen et al (1) of a 41% incidence of bone mar-

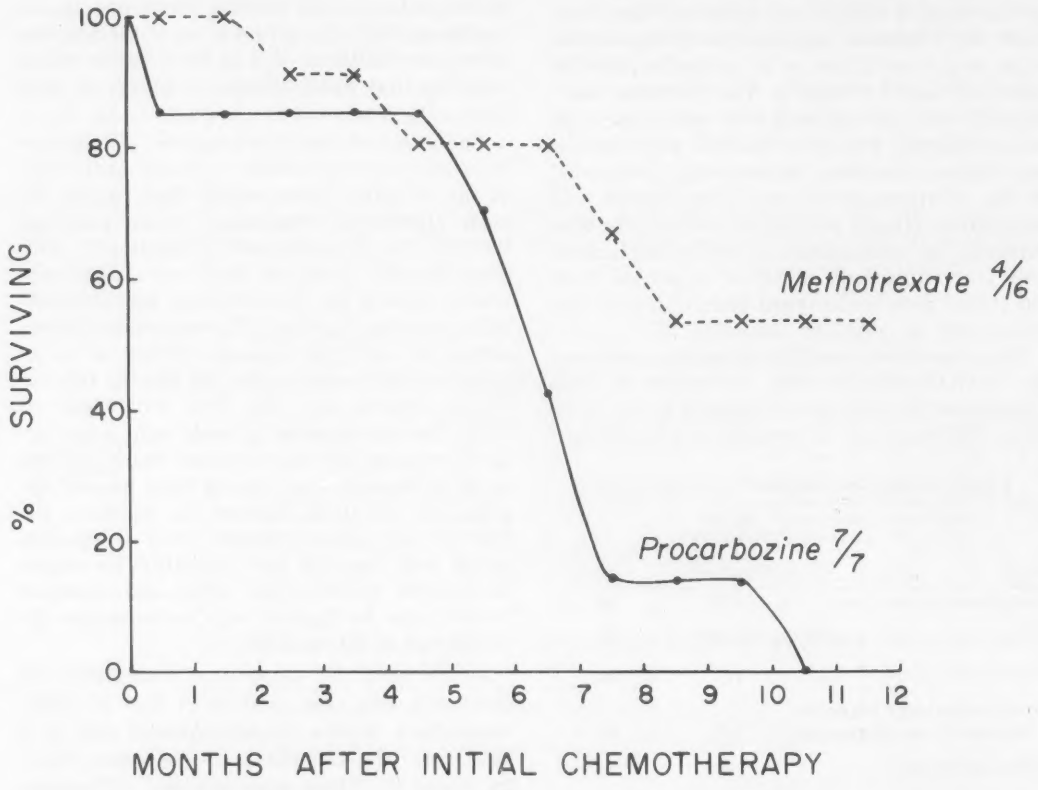

FIGURE 2.—Survival curves for patients treated in the present study.

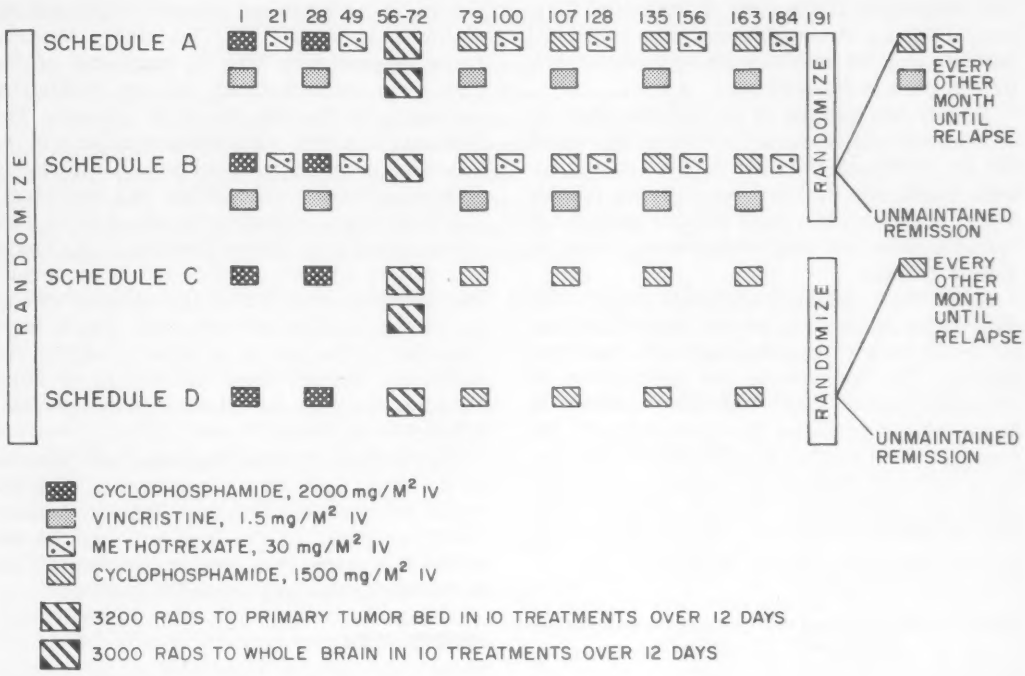
RANDOMIZE
SCHEDULE A
SCHEDULE B
SCHEDULE C
SCHEDULE D
1 21 28 49 56-72 79 100 107 128 135 156 163 184 191
RANDOMIZE
EVERY OTHER MONTH UNTIL RELAPSE
UNMAINTAINED REMISSION
RANDOMIZE
EVERY OTHER MONTH UNTIL RELAPSE
UNMAINTAINED REMISSION
CYCLOPHOSPHAMIDE, 2000 mg/M² IV
VINCRISTINE, 1.5 mg/M² IV
METHOTREXATE, 30 mg/M² IV
CYCLOPHOSPHAMIDE, 1500 mg/M² IV
3200 RADS TO PRIMARY TUMOR BED IN 10 TREATMENTS OVER 12 DAYS
3000 RADS TO WHOLE BRAIN IN 10 TREATMENTS OVER 12 DAYS

FIGURE 3.—Randomization scheme for activated phase III ALGB protocol as modified from the present study.

TABLE 3.—Remission induction

Response	No. of patients		
	Schedule I	Schedule II	Schedule III
Complete	1	4	8
Partial	6	2	2*

*Two patients are still alive and have completed only one cycle of chemotherapy ($P<0.025$).

row metastases at the time of the initial diagnosis. Bone marrow aspirations were done in 34 patients and the results were positive for malignant cells in 14 (41%).

Twenty-two percent of the patients had one or more clinically apparent abnormalities which can be attributed to tumor production of peptides (table 4). Further investigation of this aspect may provide a more reliable method for response detection with chemotherapy and radiation therapy.

In summary, we have presented preliminary data on the response to several chemotherapeutic drugs used in combination with radiation therapy. The response to the combination of cyclophosphamide and vincristine appears to represent a substantial improvement over the response to cyclophosphamide alone. Employing a technique where a third drug can be evaluated as a single agent, we have demonstrated that methotrexate appears to be of value in this disease while procarbazine probably is not.

TABLE 4.—Hormonal and neurologic syndromes attributable to small cell carcinoma

Syndrome	No. of patients
Abnormal antidiuretic hormone level	4
Eaton-Lambert syndrome	2
Hypercalcemia-hypophosphatemia	1
Gynecomastia	1
Total	8/36 (22%)

In addition, we are employing a course of radiation therapy which is biologically equivalent to standard therapy but is shorter in duration and can be successfully combined with chemotherapy. Preliminary evidence suggests that there will be a significant improvement in survival rates.

To test this concept further, the ALGB has approved a cooperative study of small cell carcinoma using combined chemotherapy and radiation therapy (fig 3). This study, designed for a homogeneous type of carcinoma of the lung, will employ many of the techniques learned in the therapy for acute leukemia. The best single agent, cyclophosphamide, will be tested against combination chemotherapy using cyclophosphamide, vincristine, and methotrexate. In addition, radiation therapy will be used therapeutically to remove the bulk of the tumor and prophylactically to prevent brain metastases. Finally, one half of the patients will be placed in unmaintained remissions. This is most important if we are to be able to employ the techniques learned from the studies of acute leukemia and from the studies of Skipper and Schabel.

Undoubtedly, further regimens will have to be developed including intensification and periodic reinduction regimens. But information about carcinoma of the lung will best be obtained if homogeneous groups of patients with carcinoma of the lung are studied.

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Monochemotherapy of Bronchogenic Carcinoma With Special Reference to Cell Type

Oleg S. Selawry [1,2,3]

SUMMARY

The responses of over 5000 patients with bronchogenic carcinoma to monochemotherapy with 31 drugs are reviewed. Seven drugs meet the minimum requirements for adequate phase II clinical trials for all four major cell types of bronchogenic carcinoma. Seven additional agents have been adequately studied in three or fewer cell types and the remaining 17 compounds have received inadequate or no studies at all. Response by cell type shows marked differences which might be therapeutically exploitable.

[Cancer Chemother Rep Part 3, vol 4:177–188, 1973]

Bronchogenic carcinoma remains the most commonly lethal form of cancer in the United States. The 5-year survival rate is below 10%. Thus, effective therapy for 90%–92% of the patients (an estimated 68,000 in 1972) (1) is lacking.

The present review includes a comprehensive summary of objective tumor response to chemotherapy with single agents. Response by major cell type is stressed because of marked differences in sensitivity of the four major microscopic types of lung cancer. It is hoped that these data will be useful for considerations of therapy, for closure of major remaining gaps of knowledge in future clinical trials, and as a basis for the planning of combination chemotherapy.

MATERIALS AND METHODS

A comprehensive literature search has been conducted since 1968, including papers on bronchogenic carcinoma and papers on chemotherapy. The search has been supplemented by Medline and Medlars.

Minimum requirements for inclusion of data in this review included all of the following: microscopic proof of bronchogenic carcinoma; progressive, objectively measurable, or evaluable cancer at the start of the treatment; no simultaneous use of other drugs or of radiotherapy to the measured lesion(s) during chemotherapy with a single agent; and measurement of size and number of tumor lesions at intervals of at least 3 weeks.

Objective response was defined as at least 25% regression of well-outlined palpable lesions or at least 50% regression of lesions on chest or bone films, using the product of the longest times the widest perpendicular diameter. Simultaneous occurrence of new lesions or progressive disease elsewhere (25% for palpable lesions, 50% for lesions on X-ray films) precluded response.

All patients who satisfied the above criteria were included as denominator for response

[1] National Cancer Institute-Veterans' Administration Medical Oncology Branch, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

[2] The invaluable and dedicated technical assistance of Thomas Welsh, Elise Mackie, and Susan Krezoski is gratefully acknowledged.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are listed in the List of Compounds at the end of the text.

rates even if they died within less than 1 week after treatment.

Optional criteria included description of cell type.

Papers including fewer than ten patients were used only when larger series were not available for a given drug and cell type.

Drug doses are given in mg/m² body surface area and/or in mg/kg. The conversion factor from mg/kg to mg/m² is approximately 35–40 for a non-obese adult patient.

A detailed description of study design and criteria for chemotherapeutic trials in patients with lung cancer is presented elsewhere in this issue (2).

RESULTS

Fifty-one percent of the reported patients received bifunctional alkylating agents (table 1). Mechlorethamine leads the list, with a response rate of 36% in 1266 patients. Response rates of individual observers varied between 0 and 68%. Treatment was usually initiated with a dose of 0.4 mg/kg (~15 mg/m²), given intravenously (iv) over 1–4 days. Two weeks after this initial course, treatment was continued with weekly doses of 0.1 mg/kg (~4 mg/m²) adjusted to individual tolerance.

Response usually lasted 1–4 months, with an average duration of approximately 2 months. Improvement of superior vena caval obstruction, described as occurring in more than 50% of the patients receiving mechlorethamine, is not included in the response figures for this or other drugs.

Cyclophosphamide, the most widely used alkylating agent for chemotherapy of solid tumors, shows a response rate of 23%. Authors using widely spaced doses of 800–4000 (!) mg/m² (20–100 mg/kg) given iv every 2–3 weeks report higher response rates than those using 100–200 mg/m²/day given orally (table 37 of ref 144) or weekly doses. The evidence in favor of widely spaced doses is suggestive but inconclusive in the absence of a published comparative clinical trial.

ThioTEPA, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC–45388), and melphalan have marginal activity. Busulfan and chlorambucil are only questionably active.

Mitomycin C and adriamycin lead the list of tumor inhibitory antibiotics, with response rates of 23% and 20% respectively (table 2). Mitomycin C was usually given in courses of 0.05 mg/kg/day iv (~1.75–2.0 mg/m²) for 6 days, followed by treatment every other day, or in courses of 10 days. Adriamycin was given in doses of 20 mg/m²/day iv for 3 days with repeat courses every 3 weeks to a maximal total dose of 500–600 mg because higher total doses are fraught with an increasing risk of irreversible cardiotoxicity (alternate schedule: 60–75 mg/m² every 3 weeks).

Streptonigrin is marginally active. Daunorubicin and porfiromycin, close analogs of adriamycin and mitomycin C respectively are only questionably active, as is bleomycin. Actinomycin D and mithramycin appear inactive, except for symptomatic control of hypercalcemia.

TABLE 1.—Objective response to bifunctional alkylating agents

Drug	Responses (%)		No. of patients treated	Reference No.
	All patients	Range of response rates		
Mechlorethamine	36	0–68	1266	3–32
Cyclophosphamide	23	10–63	814	6,14,28,33–51
ThioTEPA	15	7–32	141	14,17,32,52,53
NSC-45388	12	10–25	109	54–56
Melphalan	11	—	38	57
Busulfan	9	7–21	169	58
Chlorambucil	5	—	21	59,60

Substances of plant origin have received inadequate attention, except for vinblastine which had marginal activity of 11% (table 3). The paucity of data on vincristine and the podophyllotoxin derivatives is particularly striking because of their widespread use here (vincristine) and abroad (both drugs). Emetine deserves further attention as a nonmyelosuppressive agent.

Two nitrosoureas and methotrexate lead the list of other active agents, with response rates of 25% or better (table 4). 1-Methyl-1-nitrosourea is an experimental agent which showed response rates of 22% and 43% respectively, in two reports by reputable Soviet investigators.

CCNU shows activity similar to 1-methyl-1-nitrosourea in contrast to the closely related BCNU. This high activity of CCNU is of particular interest because it is not cross-resistant against bifunctional alkylating agents in patients with Hodgkin's disease.

Methotrexate retains usually short-lasting activity in 25% of the patients with a wide range of response rates. A review of the literature fails to establish an optimal dose schedule for either induction or maintenance of response. The current trend is toward spaced doses (20–30 mg/m² twice weekly or 40–60 mg/m²/week given orally or iv) and toward loading doses (1.25 mg given orally qid to toxicity or 12–15 mg/m²/day for 4 days). A discussion of combined use of methotrexate followed by leucovorin exceeds the scope of this review.

Hexamethylmelamine is of interest because of impressive correlations between response and duration of survival (113). Thus, one complete responder lived 33 months. Twelve patients who had partial responses had a median survival of 8.5 months. The 16 patients with static disease lived 6 months and the 41 patients with progressive disease died within a median of 2.6 months. The drug is given in daily oral increments of 8–12 mg/kg or 300–450 mg/m². Interest in hexamethylmelamine would be further augmented if it proved to be non-cross-resistant with bifunctional alkylat-

TABLE 2.—Objective response to antibiotics

Drug	Responses (%)		No. of patients treated	Reference No.
	All patients	Range of response rates		
Mitomycin C	23	8–27	185	61–63
Adriamycin	20	0–50	147	64–67
Streptonigrin	11	0–29	53	68–70
Bleomycin	8	0–20	130	71–75
Daunorubicin	7	—	14	76
Porfiromycin	7	—	42	77–78
Actinomycin D	0	—	16	79
Mithramycin	0	—	23	79,80

TABLE 3.—Objective response to agents of plant origin

Drug	Responses (%)		No. of patients treated	Reference No.
	All patients	Range of response rates		
Emetine	33	—	6	81
Vincristine	33	—	6	82
Vinblastine	11	0–20	151	83–94
Colchicine	3	0–4	30	95–96

TABLE 4.—Objective response to miscellaneous agents

Drug	Responses (%)		No. of patients treated	Reference No.
	All patients	Range of response rates		
1-Methyl-1-nitrosourea	34	22–43	76	97,98
CCNU	27	18–40	85	99–101
Methotrexate	25	3–43	395	102–112
Hexamethylmelamine	20	10–30	372	113–119,144
Procarbazine	18	6–27	159	120–124
Hydroxyurea	17	0–26	84	125–129
5-FUDR	12	—	25	130
BCNU	8	0–12	72	33,131,132
5-Fluorouracil	7	0–36	157	92,133–139
6-Mercaptopurine	3	0–4	105	140–142
Cytosine arabinoside	0	0	19	92,143

ing agents; preclinical data are controversial, clinical data are lacking.

Procarbazine and hydroxyurea have definite activity. 5-Fluorouracil is only questionably active.

Description of objective response in bronchogenic carcinoma is only of limited value, because response rates differ as much for each major cell type of lung cancer as they would for different types of leukemia or of malignant lymphomas.

CCNU leads the list of agents active against epidermoid (squamous cell) carcinoma, followed by mechlorethamine, methotrexate, adriamycin, procarbazine, and cyclophosphamide (table 5). The apparent superiority of CCNU over BCNU is striking. The ranking of mechlorethamine over cyclophosphamide is in agreement with survival data in a major controlled clinical trial. Patients with epidermoid carcinoma had a statistically significant doubling of median survival from 3 months (placebo) to 6 months (mechlorethamine), while cyclophosphamide failed to prolong median survival (placebo, 2.6 months; cyclophosphamide, 2.7 months) (45). Vinblastine exhibits a 16% response rate. Bleomycin defies its reputation as an effective agent against epidermoid carcinoma, despite uptake of the drug by pulmonary tissue and organotropic toxicity of pulmonary fibrosis.

TABLE 5.—Objective response of epidermoid carcinoma

Drug	Responses (%)	No. of patients treated
CCNU	41	29
Mechlorethamine	33	111
Methotrexate	25	140
Adriamycin	24	45
Procarbazine	20	30
Cyclophosphamide	19	183
Vinblastine	16	20
1-Methyl-1-nitrosourea	15	13
Hexamethylmelamine	11	99
Bleomycin	9	75
Busulfan	7	61
BCNU	3	38
Colchicine	0	11
6-Mercaptopurine	0	16
Mitomycin C	0	22
Streptonigrin	0	10

Small cell carcinoma (with oat cell carcinoma as a major subgroup) is the most sensitive type of bronchogenic carcinoma, with reported response rates of 50% or better for as heterogenous a group of drugs as 1-methyl-1-nitrosourea, procarbazine, methotrexate, and cyclophosphamide (table 6). Mechlorethamine, hexamethylmelamine, adriamycin, and BCNU are definitely active. Sporadic clinical trials imply activity of a wide variety of drugs such as emetine (a nonmyelosuppressive agent) and 6-mercaptopurine, each including complete tu-

mor regressions, and the vinca alkaloids (table 7). Bleomycin is the only drug with established inactivity against small cell carcinoma.

Adenocarcinoma responds to methotrexate, hexamethylmelamine, mechlorethamine, mitomycin C, and CCNU (table 8). Objective response in small groups of patients is summarized in table 9. The lack of data on 5-fluorouracil is surprising because of the established value of this drug for treatment of adenocarcinoma of the breast, stomach, pancreas, colon, and rectum.

Procarbazine leads the list of agents effective against large cell anaplastic carcinoma (table 10), followed by mechlorethamine, cyclophosphamide, hexamethylmelamine, and CCNU. Methotrexate is marginally active; BCNU is probably ineffective. Sporadic data on response to adriamycin, busulfan, streptonigrin, and vinblastine are summarized in table 11.

TABLE 6.—Objective response of small cell carcinoma

Drug	Responses (%)	No. of patients treated
1-Methyl-1-nitrosourea	78	18*
Procarbazine	67	12
Cyclophosphamide	50	120
Methotrexate	50	20
Mechlorethamine	39	51
Hexamethylmelamine	36	67
Adriamycin	29	17
BCNU	20	15
Busulfan	18	17
CCNU	13	15
Bleomycin	0	24

*Includes large cell anaplastic carcinoma.

TABLE 7.—Objective response of small cell carcinoma (<10 observations)

Drug	No. of responses	No. of patients treated
Emetine	CR*	2
6-Mercaptopurine	CR	9
Vinblastine	3†	9
Vincristine	2	6

*CR = complete regression.

†Three patients survived for 1+ years (no measurements given).

TABLE 8.—Objective response of adenocarcinoma

Drug	Responses (%)	No. of patients treated
Methotrexate	32	25
Mechlorethamine	29	80
Mitomycin C	27	11
CCNU	24	21
Hexamethylmelamine	20	34
Procarbazine	19	16
Cyclophosphamide	17	12
Busulfan	4	28
BCNU	0	14

DISCUSSION

Twenty-five years of chemotherapy with single drugs in more than 5000 patients with bronchogenic carcinoma permits a number of cautious generalizations:

TABLE 9.—Objective response of adenocarcinoma (<10 observations)

Drug	No. of patients	
	Responding	Treated
Adriamycin	1	6
Bleomycin	2	9
Colchicine	1	7
Emetine	1	2
Vinblastine	1	6

TABLE 10.—Objective response of large cell carcinoma

Drug	Responses (%)	No. of patients treated
Procarbazine	35	17
Mechlorethamine	27	129
Cyclophosphamide	23	22
Hexamethylmelamine	17	37
CCNU	15	19
Methotrexate	12	104
BCNU	7	15
6-Mercaptopurine	3	29
Colchicine	0	12

TABLE 11.—Objective response of large cell carcinoma (<10 observations)

Drug	No. of patients	
	Responding	Treated
Adriamycin	2	3
Busulfan	1	6
Streptonigrin	1	7
Vinblastine	2	2

1. Response rates of 20% or better are noted for at least three chemotherapeutic agents per major cell type of bronchogenic carcinoma. These response rates are comparable to agents such as 5-fluorouracil in cancer of the breast and colon (145).
2. Chemotherapeutic agents show marked differences in activity against the four major types of bronchogenic carcinoma (table 12). Thus, CCNU appears to be the most active drug against epidermoid carcinoma. 1-Methyl-1-nitrosourea and procarbazine lead the list for small cell carcinoma; methotrexate and mechlorethamine are the frontrunners in adenocarcinoma, and procarbazine and mechlorethamine have the highest response rates in large cell carcinoma.
3. Small cell carcinoma is by far the most sensitive type of lung cancer, as seen by response rates of 50% or better with four different drugs. This high response rate offers promise for combination chemotherapy, as reported elsewhere in this issue (146) and in the literature.
4. Members of the same class of agents show marked differences in activity against the four major cell types. This is particularly evident for bifunctional alkylating agents and for nitrosoureas.
5. Major gaps of knowledge remain to be closed. Thus, only seven of some 31 more common antineoplastic agents fulfilled minimum requirements of an adequate clinical trial in all four cell types of lung cancer. Seven additional drugs were studied in at least one to three cell types and the remaining 17 drugs received inadequate trials or no trials at all with reports by cell type (table 13).

The "adequately" studied drugs include BCNU, CCNU, cyclophosphamide, mechlorethamine, hexamethylmelamine, methotrexate, and procarbazine. Inadequately studied drugs include such newcomers as adriamycin, where adequate published data can be expected within 1–2 years, and such widely used drugs as 5-fluorouracil and the vinca alkaloids. A concerted effort should be made to close these gaps through publication of available data or through formal phase II studies of therapeutic efficacy.

The minimum requirements for "adequate studies" include at least 14 evaluable patients per cell type in order to avoid false negative results with a probability of $P = 0.05$ (147). Positive results, for the purposes of this review, were accepted if two or more of 14 or fewer patients responded or if the response rate in a larger series exceeded 8%. This arbitrary definition might compensate for spurious "responses" related to clearance of an atelectasis or a pneumonic infiltrate.

6. The comparative response rates given in this paper should be regarded as preliminary and open to change, pending controlled clinical trials and correction for such factors as stage of disease, immunologic status, and performance of the patient. The impact of stage of disease is exemplified in a study

TABLE 12.—Ranking of response rates by cell type

Drug	Ranking by cell type			
	Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma	Large cell carcinoma
CCNU	1	8	4	5
Mechlorethamine	2	4	2	2
Methotrexate	3	3	1	6
Adriamycin	4	6		
Procarbazine	5	2	6	1
Cyclophosphamide	6	3	7	3
1-Methyl-1-nitrosourea	7	1		
Hexamethylmelamine	8	5	5	4
BCNU	9	7	8	7
Mitomycin C	10		3	

TABLE 13.—Agents with unknown activity against one or more major types of lung cancer

Drug	Effect unknown against—*			
	Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma	Large cell carcinoma
Bifunctional alkylating agents				
Busulfan	+	+	+	+
Chlorambucil	+	+	+	+
NSC-45388		+	+	+
ThioTEPA	+	+	+	+
Antibiotics				
Adriamycin			+	+
Bleomycin				+
Daunorubicin	+	+	+	+
Actinomycin D	+	+	+	+
Mithramycin	+	+	+	+
Mitomycin C/porfiromycin		+		+
Streptonigrin	+	+	+	+
Streptozotocin	+	+	+	+
Agents of plant origin				
Colchicine derivatives		+	+	
Emetine	+	+	+	+
Podophyllotoxin derivatives	+	+	+	+
Vinblastine			+	
Vincristine	+		+	+
Miscellaneous				
Cytosine arabinoside	+	+	+	+
5-Fluorouracil	+	+	+	+
Hydroxyurea	+	+	+	+
L-Asparaginase	+	+	+	+
Methyl-CCNU		+	+	+
1-Methyl-1-nitrosourea		§.	+	+
6-Mercaptopurine		+	+	

*Unknown activity is defined as negative data on <14 patients per cell type or objective response in <2 of <14 patients.

§Data reported as "anaplastic carcinoma."

with CCNU, where 12 of 17 (70%) patients with regional lymphatic metastases responded, as opposed to six of 32 (19%) responders among patients with hematogenous metastases (101). The same study includes a response rate of 70% in 35 patients with positive (≥1 cm) delayed hypersensitivity reactions of the skin, as opposed to a 5% response rate among the 18 nonreactive patients.

Finally, it should be noted that response data described in this paper are, at times, at variance with two previous publications (146, 148) because additional and, at times, more critical information has become available.

LIST OF COMPOUNDS

Actinomycin D: NSC-3053

Adriamycin: NSC-123127

BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-

Bleomycin: NSC-125066

Busulfan: NSC-750; CAS reg. No. 55-98-1; 1,4-butanediol, dimethanesulfonate

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Chlorambucil: NSC-3088; CAS reg. No. 305-03-3; butyric acid, 4-[*p*-[bis(2-chloroethyl) amino]phenyl]-

Colchicine: NSC-757; CAS reg. No. 7006-15-7

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride

Daunorubicin: NSC-83142; CAS reg. No. 23541-50-6

Emetine: NSC-33669

5-FUDR: NSC-27640; 5-fluoro-2′-deoxyuridine

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8

Hexamethylmelamine: NSC-13875; CAS reg. No. 645-05-6

Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1

Leucovorin: NSC-3590; CAS reg. No. 6035-86-5; glutamic acid, *N*-[*p*-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt

Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride

Melphalan: NSC-8806; CAS reg. No. 3223-07-2; alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, monohydrochloride, L-

6-Mercaptopurine: NSC-755; CAS reg. No. 6112-76-1; purine-6-thiol, monohydrate

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl] methylamino]benzoyl]-

1-Methyl-1-nitrosourea: NSC-23909; CAS reg. No. 684-93-5

Mithramycin: NSC-24559; CAS reg. No. 18378-89-7

Mitomycin C: NSC-26980; CAS reg. No. 50-07-7

NSC-45388; CAS reg. No. 4342-03-4; imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-

Porfiromycin: NSC-56410; CAS reg. No. 801-52-5; carbamic acid, ester with 6-amino-1,1*a*,2,8,8*a*,8*b*-hexahydro-8-(hydromethyl)-8amethoxy-1,5-dimethylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione

Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride

Streptonigrin: NSC-45383; CAS reg. No. 632-62-2

ThioTEPA: NSC-6396; CAS reg. No. 52-24-4; phosphine sulfide, tris(1-aziridinyl)-

Vinblastine: NSC-49842; CAS reg. No. 6449-03-2; vincaleukoblastine, sulfate (1:1), monohydrate

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Rationale of Combination Chemotherapy Based on Preclinical Experiments

Abraham Goldin [1]

The primary objective of the investigations of combination chemotherapy against tumor is to uncover more effective modalities of treatment. A number of combinations of drugs have now been demonstrated to provide effective therapies and possible therapeutic advantage over individual drugs in the clinic and this has stimulated considerable interest and relatively extensive clinical investigation of a variety of combination modalities. It is the responsibility of the preclinical investigator to keep apace with this effort, and, through preclinical chemotherapeutic investigations, to identify potentially useful combinations of drugs with a high likelihood of therapeutic effectiveness in the clinic and to investigate modalities of therapy with these combinations from the point of view of contributing to their optimal utilization.

I. TUMOR SYSTEMS AND COMBINATIONS SHOWING THERAPEUTIC SYNERGISM

Most of the preclinical combination studies have been conducted with the L1210 leukemia system in mice, which for individual drugs has been demonstrated to be quite useful both in the selection of compounds with high potential for clinical effectiveness and in the further preclinical investigation of optimal modalities of therapy (1, 2). Even though it has not as yet been definitively determined that the L1210 system will provide a highly appropriate model for the selection of new drug combinations for the clinic, it would appear to be reasonable to think that this would be possible particularly in view of the success to date in the prediction of activity for individual drugs. Also, some of the combinations of drugs which appear to provide an advantage in the therapy of acute lymphocytic and myelocytic leukemia have likewise been found to be therapeutically synergistic in the L1210 leukemia system (3).

There are a large number of two-drug combinations that are therapeutically synergistic in the L1210 leukemia system. With these combinations of drugs greater increases in survival time of the leukemic animals have been observed than when the drugs are employed individually on optimal schedules. Some of these combinations have been in clinical trial, but many of them have not as yet been tested in the clinic. The question of whether L1210 leukemia does indeed provide a good predicting system for the selection of combinations of drugs is surely an initial task worthy of determination.

A listing of activity in the L1210 leukemia system for combinations of drugs in clinical trial against lung cancer is presented in table 1. It is clear that there are wide gaps in the animal data.[2]

A number of additional combinations of drugs evidencing therapeutic synergism in the L1210 leukemia system and of potential clinical interest against lung cancer in man are given in table 2. One of the combinations, cytosine arabinoside plus CCNU, yielded a high percentage of leukemia-free survivors when treatment of intravenously inoculated leukemia was initiated 48 hours prior to death of controls (4).[3]

Other systems such as the Lewis lung carcinoma and B16 melanoma are also being investigated from the point of view of their usefulness in the selection and study of combinations of antitumor agents. Therapeutic synergism was obtained with the combination of cyclophospha-

[1] Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md.

[2] Combinations listed as "no data" are currently under test in the L1210 leukemia and Lewis lung carcinoma systems.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

TABLE 1.—Combinations of drugs in clinical trial: Lung cancer

Drugs	Therapeutic synergism, L1210*		
	Early ip	Advanced sc	Iv
Cyclophosphamide + methotrexate		+	
Cyclophosphamide + CCNU			+
Cyclophosphamide + hydroxyurea	–		–
CCNU + mechlorethamine		No data	
Cyclophosphamide + methyl-CCNU		±	+
Bleomycin + vincristine	–		
Actinomycin D + vincristine		No data	
Cyclophosphamide + hexamethylmelamine		No data	
Methotrexate + hexamethylmelamine		No data	
Methotrexate + mechlorethamine		No data	
Procarbazine + vincristine		No data	
CCNU + cyclophosphamide + methotrexate		No data	
CCNU + mechlorethamine + methotrexate		No data	
Procarbazine + vincristine + hydroxyurea		No data	

*L1210 observations from NCI and Microbiological Associates, Bethesda, Md, and Southern Research Institute, Birmingham, Ala. – = no activity, ± = equivocal activity, + = activity.

TABLE 2.—Some combinations of drugs therapeutically synergistic against leukemia L1210: Potential candidates against lung cancer*

Methotrexate + BCNU
Methotrexate + cytosine arabinoside
Methotrexate + methyl-GAG
Methotrexate + 1-methyl-1-nitrosourea
Methotrexate + 5-FU or 5-FUDR
Methotrexate + actinomycin D
Methotrexate + 6-MP
Methotrexate + guanazole
Methotrexate + camptothecin
Cyclophosphamide + NSC-45388
Cyclophosphamide + NSC-82196
Cyclophosphamide + cytosine arabinoside
Cyclophosphamide + BCNU
Cyclophosphamide + 6-MP
Cyclophosphamide + *cis*-diamminedichloroplatinum
Isophosphamide + *cis*-diamminedichloroplatinum

TABLE 2.—Some combinations of drugs therapeutically synergistic against leukemia L1210: Potential candidates against lung cancer*—Continued

NSC-45388 + adriamycin
Cytosine arabinoside + procarbazine
Cytosine arabinoside + 6-thioguanine
6-MP + CCNU
6-MP + daunorubicin
Cytosine arabinoside + hydroxyurea
ICRF-159 + daunorubicin or adriamycin
Cytosine arabinoside + CCNU

*Observations from NCI and Microbiological Associates, Bethesda, Md, and Southern Research Institute, Birmingham, Ala.

TABLE 3.—Therapeutic synergism against established Lewis lung tumor with a combination of cyclophosphamide plus methyl-CCNU*

Agent	Dose† (mg/kg)	ILS (%)	Day 75 S/T
Cyclophosphamide	225	50	0/10
Methyl-CCNU	24	57	2/20
Cyclophosphamide + methyl-CCNU	150 + 24	>168	16/20

*Adapted from JG Mayo, et al. Cancer Chemother Rep 56:183–195, 1972 (ref 5). ILS = increase in lifespan; S/T = No. of survivors/No. treated.

†Single treatment Day 7. Local tumor 400 mg.

mide plus methyl-CCNU in the treatment of established Lewis lung tumor, involving bronchial dissemination, with respect to regression of local tumor, survival time, and percentage of cures (table 3) (5). Therapeutic synergism has also been observed with this combination in the B16 melanoma system (DP Griswold, Jr, cited in reference 5).

Systems such as L1210 leukemia would appear to be useful in the determination of optimal modalities of therapy and for the establishment of principles pertaining to combination chemotherapy. Definition of the factors influencing the effectiveness of combinations of drugs may result in the identification of optimal therapeutic modalities.

II. BASIS FOR IMPROVED THERAPEUTIC RESPONSE WITH COMBINATION CHEMOTHERAPY

A. Increase in Antitumor Effectiveness Without a Proportionate Increase in Limiting Toxicity for the Host

The choice of drugs for combination chemotherapy is of primary importance. In general, the combinations of drugs tested preclinically and clinically have been those which have demonstrated antitumor activity individually. It has been considered that where the drugs have differing fundamental mechanisms of action there may be a proportionate increase in antitumor effectiveness relative to any increase in

host toxicity (6–9). This would permit the employment of the combination of drugs at reduced risk for the host (increased therapeutic index). It would also permit the employment of higher dosage of drug with overall increased therapeutic response (therapeutic synergism) (6–11).

It is possible to select drugs on the basis of biochemical rationale involving knowledge concerning the action of the drugs on metabolic pathways. One such study utilized treatment with methotrexate plus 5-fluorouracil (5-FU) forming a blockade in the pathway of DNA synthesis. The combination was more effective than either drug alone in increasing survival time of mice with L1210 leukemia (12).

Other examples involve treatment of L1210 leukemia with cytosine arabinoside plus either hydroxyurea, 5-hydroxypicolinaldehyde thiosemicarbazone, or guanazole, in which there is a combination blockade of DNA polymerase and ribonucleotide reductase. Therapeutic synergism against L1210 leukemia was observed on treatment with cytosine arabinoside plus each of the ribonucleotide reductase inhibitors. Data for cytosine arabinoside plus hydroxyurea are summarized in table 4 (13).

B. Decrease in Host Toxicity Without a Proportionate Loss in Antitumor Effectiveness

One way in which combinations of drugs may be employed is in an attempt to diminish host toxicity with retention of antitumor effectiveness. This was observed in the L1210 system on utilization of delayed citrovorum factor in combination with methotrexate (10, 14). With the combination of methotrexate plus delayed citrovorum factor it was possible to increase the dose of the antagonist and to obtain a more extensive therapeutic effect. Detailed investigation of the temporal relationships of administration of other metabolite-antimetabolite combinations may provide additional therapeutic combinations of this nature.

It is also possible for differential protection for the host to occur with a combination of two antitumor agents, where one of the drugs reduces the toxicity of the second drug. An example of this is provided by the combination of cytosine arabinoside plus 6-thioguanine in which cytosine arabinoside appeared to protect against 6-thioguanine toxicity. The combination was therapeutically synergistic against L1210 leukemia, and the high incidence of tumor-free survivors appeared to be attributable to the cytosine arabinoside protection against 6-thioguanine toxicity (table 5) (15). A similar result was obtained for treatment of L1210 leukemia with a combination of ICRF-159 plus daunorubicin (table 6) (16).

There is the possibility of protecting with an ineffective agent against the host toxicity of an antitumor agent, without reversal of therapeutic action. An example of this is provided by the utilization of *N*-acetylcysteine in combination with isophosphamide (table 7) (8, 17).

C. Identification of Optimal Dosages and Dosage Ratios

As with individual drugs, the effectiveness of drug combinations may be influenced by the dosages employed. In addition, the choice of appropriate ratios in which the drugs are used may improve the therapeutic outcome. The com-

TABLE 4.—Therapeutic synergism in the treatment of leukemia L1210 (ip) with cytosine arabinoside plus hydroxyurea*

Treatment†	Highest nonlethal dose	ILS (%)	60-Day S/T
Cytosine arabinoside alone	15	271	0/10
Hydroxyurea alone	60	42	0/10
Cytosine arabinoside + hydroxyurea	10 + 40	>750	6/10

*Data of FM Schabel, Jr, et al. Proc Am Assoc Cancer Res 12:67, 1971 (ref 13).
† Treatment ip, q3h × 8, Days 2,6,10,14.

TABLE 5.—Therapeutic synergism with cytosine arabinoside plus 6-thioguanine in the treatment of leukemia L1210*

Treatment†	Optimal dose (mg/kg)	ILS (%)	S/T
Cytosine arabinoside alone	15	480	0/30
6-Thioguanine alone	1.0	125	0/20
Cytosine arabinoside + 6-thioguanine	15 + 1.0	604	9/18

*Data of LH Schmidt and FM Schabel, Jr. See also LH Schmidt, et al. Proc Am Assoc Cancer Res 11:70, 1970 (ref 15). Leukemic inoculum 10^6 cells iv.

† Treatment q3h/24 hr, Days 1,5,9,13.

TABLE 6.—Therapeutic synergism of early leukemia L1210 on treatment with ICRF-159 plus daunorubicin*

Treatment†	Optimal dose (mg/kg)	ILS (%)	S/T
Daunorubicin alone	2.0	22	0/8
ICRF-159 alone	400	55	0/8
Daunorubicin + ICRF-159	2.0 + 400	>500	4/8

*Data of RJ Woodman, et al. Proc Am Assoc Cancer Res 13:31, 1972 (ref 16).

† Treatment ip, q4d, Days 1,5,9.

TABLE 7.—Influence of *N*-acetylcysteine on the antileukemic (L1210) effectiveness of isophosphamide*

Treatment†	Optimal dose (mg/kg)	MST‡	S/T
Isophosphamide alone	300	23.5	3/8
N-Acetylcysteine alone	750–1000	9.0	0/8
Isophosphamide + *N*-acetylcysteine	500 + 1500	>90	8/8
Control	—	9.0	

*Data of I Kline, et al. Proc Am Assoc Cancer Res 13:29, 1972 (ref 17); and A Goldin, et al (ref 8). Tumor inoculated ip.

† Treatment ip, Day 1 only.

‡ MST = median survival time.

bination may evidence marked therapeutic synergism when employed on an optimal ratio and be less effective or ineffective at other ratios. In one study the optimal ratio for therapeutic synergism in the L1210 system was 33% methyl-GAG plus 67% 6-mercaptopurine (6-MP) on an mg/kg basis (7). In another study optimal therapy was obtained with a ratio of 83.3% ICRF-159 to 16.7% camptothecin in mg/kg (unpublished data cited in reference 8).

D. Determination of Optimal Scheduling

Schedule dependency may be demonstrated for combinations of drugs in the same manner as for individual drugs and the identification of optimal scheduling is important for the improvement of therapy. Such schedule dependency has been reported in the L1210 system for the combination of 6-MP plus azaserine (18). Therapeutic synergism was observed with this

combination on treatment every 2 days. It was diminished on daily administration and was not evident on twice daily treatment. In another example, the combination of ICRF-159 and *cis*-diamminedichloroplatinum was observed to be schedule dependent (19). In combination treatment with the drugs on an every-4-day schedule, therapeutic synergism was observed against L1210 leukemia. The synergism was not evident however when ICRF-159, administered q3h/24 hr every 4 days, was combined with *cis*-diamminedichloroplatinum every 4 days. Failure of synergism occurred in the latter instance despite the fact that ICRF-159 when employed alone was optimally effective when given on the q3h/24 hr every-4-day schedule.

It should be noted, as illustrated in the latter example, that the optimal schedules for combinations of drugs may not necessarily be the same as the optimal schedules for the individual drugs.

In the adjustment of schedules for combinations of drugs one should take into consideration the limiting factors in the utilization of the drugs when employed individually. With a drug such as adriamycin, for example, where the toxicity becomes limiting very rapidly, one procedure could be to treat maximally for a short time (1 day in the case of adriamycin) and then follow with more prolonged therapy with a second drug such as methotrexate or 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC-45388) (20,21).

E. Delay in Origin and Treatment of Tumor Cell Resistance

Another major factor in the utilization of combinations of drugs is the possible avoidance of the origin of tumor cell resistance to chemotherapy. It is not clear to what extent biochemical resistance interferes with the utilization of drugs in the clinic. Nevertheless, the patients do become resistant to chemotherapy and there is the possibility that with combinations of drugs the origin of resistance may be avoided or delayed. In one model with L1210 leukemia (7) it was found that the synergistic combination of methotrexate plus the terephthalanilide derivative NSC-60339 delayed the onset of resistance to the drugs. Also, once resistance has occurred the possibility exists that with combinations of drugs more effective therapy may result. It has been observed that the origin of resistance may lead to increased sensitivity to a second drug (collateral sensitivity). This occurred, for example, with a 6-MP-resistant line of L1210 leukemia which became collaterally sensitive to methotrexate (22). Where it is known that resistance to a drug occurs very rapidly it may be advisable to use combination chemotherapy quite early during the course of treatment.

F. Treatment of Sequestered Tumor Cells

With respect to tumor cell sequestration, either in the brain, lung, or other organs, an additional problem arises in therapy. Drugs such as BCNU and cytosine arabinoside are capable of crossing the blood-brain barrier and increasing the survival time of leukemic mice with intracranial leukemia. In combination they have been demonstrated to be therapeutically synergistic against L1210 leukemia and their action has been attributed at least in part to their ability to cross the blood-brain barrier (23). The combination of ICRF-159 plus cytosine arabinoside has been shown to be therapeutically synergistic against intracranially inoculated L1210 leukemia (8). Combinations of drugs should be sought which may also be more effective against tumor cells in the lung and other sequestered sites. The combination of cyclophosphamide and methyl-CCNU, synergistically effective against advanced Lewis lung tumor, cited above (5), may provide such an example.

G. Tumor Cell Synchronization

Priming-dose therapy may be utilized in an attempt to synchronize the tumor cell population to render it more susceptible to a cell cycle-specific (CCS) agent at the time when the cells traverse S phase. This occurred with vinblastine or demecolcine followed by treatment with cytosine arabinoside (24).

H. Priming-Dose Chemotherapy of Advanced Tumor

The body burden of tumor cells may influence the effectiveness of combination chemotherapy,

just as it influences the effectiveness of individual drugs. The combination of daily treatment with NSC-45388 plus 5-FU showed therapeutic synergism against L1210 leukemia when treatment was started 1 day after leukemic inoculation. However, when treatment was started on the fifth day the effectiveness of therapy was diminished (25).

Where the body burden of tumor is great there may be an advantage in sharp priming chemotherapy with a cytotoxic agent followed by more prolonged treatment with a second drug. There are a number of instances in which priming dose chemotherapy has been highly useful and examples are given in table 8 (3). Schabel (26) and Laster et al (27) found that a single treatment with cyclophosphamide followed by a course of 6-MP given daily resulted in cures of Carcinoma 755. The cure rate was further increased when the regimen was repeated. The priming dose in these instances is intended to reduce the body burden of tumor cells to the point where the second drug may be more effective. The priming drug may be a cell cycle stage-nonspecific (CCNS) agent, whereas the more prolonged ensuing therapy may be with a CCS agent. The priming therapy, by reducing the tumor cell population, may increase the proportion of cells that are actively dividing, thereby exposing these cells more effectively to a CCS agent.

Whole body irradiation, or irradiation of a local tumor mass, followed by chemotherapy could be included as a form of "priming-dose" therapy.

TABLE 8.—Therapeutic synergism on sequential treatment of advanced leukemia L1210*

Priming drug	Second drug
6-MP	Methotrexate every 4 days
BCNU	6-MP every 2 days
Cyclophosphamide	Methotrexate daily or every 4 days
BCNU	Methotrexate daily, every 2 days, or every 4 days
5-FU	Methotrexate daily or every 4 days
Cyclophosphamide	Cytosine arabinoside 4 times daily
Cyclophosphamide	Bromochloromethotrexate every 4 days
Cyclophosphamide	Dichloromethotrexate every 4 days
BCNU	Cytosine arabinoside daily, every 2 days, or every 4 days.

*From A Goldin, et al. Cancer Chemother Rep 55:309–507, 1971 (ref 3).

I. Surgery plus Chemotherapy

Alternatively, where there is a large localized mass of tumor cells in addition to systemic disease, surgery plus chemotherapy may be the modality of choice. Here too, reduction of the body burden of tumor cells by surgery and the subsequent increase in the pool of actively dividing cells may markedly improve therapeutic effectiveness (28). Mayo et al (5) (table 9) observed that surgery of advanced Lewis lung carcinoma when followed by treatment with methyl-CCNU plus cyclophosphamide was highly effective in producing long-term tumor-free survivors. This modality was more effective than surgery plus the individual drugs and more effective than the synergistic combination of methyl-CCNU plus cyclophosphamide.

J. Immunotherapy plus Chemotherapy

The possibilities for the combination of immunotherapy plus chemotherapy have been essentially untapped. It may be mentioned that the alteration of tumor cell immunogenicity by chemotherapeutic agents (29) may in turn per-

TABLE 9.—Response of Lewis lung carcinoma to surgery plus methyl-CCNU plus cyclophosphamide*

Treatment†	Percentage of long-term survivors	
	Chemotherapy alone	Chemotherapy + surgery
Methyl-CCNU	1	30
Cyclophosphamide	0	35
Methyl-CCNU + cyclophosphamide	24	70‡

*Data of JG Mayo, et al. Cancer Chemother Rep 56:183–195, 1972 (ref 5).

†Treatment on 12th day after sc implantation.

‡Experiment still in progress.

mit a host immune response to cooperate with antitumor chemotherapy. Included in this category could be nonspecific immunologic stimulation as with BCG, and adoptive immunologic procedures as with allogeneic or syngeneic immune cells and active or passive immunization.

K. Other Possibilities for Combination Modalities

Drug combinations may be sought which prevent tumor cell infiltration and metastasis or which are active against tumorigenic virus or viral-induced tumors. Drugs may be found which stimulate cells in G_0 to divide rendering them more susceptible to conventional chemotherapeutic agents. Drugs may be sought which improve distribution, prevent detoxification, or maintain tissue levels of the primary antitumor agent. Drugs may also be found which prevent immunosuppression by the antitumor drug.

III. MULTIPLE DRUG COMBINATION CHEMOTHERAPY

There is now very strong interest in multiple-drug combination chemotherapy where combinations of three or more drugs are employed in various ratios and on varying schedules. There is great difficulty in the examination of a large series of combinations utilizing highly balanced experimental designs because of the great number of animals required. Several balanced model experiments with L1210 leukemia have been conducted with combinations of three drugs. The triple combination of methotrexate plus cyclophosphamide plus BCNU was not more effective than the double combination of cyclophosphamide plus BCNU or BCNU alone (30). However, the triple combination of mitomycin C plus 5-FU plus cytosine arabinoside did yield therapeutic synergism (31).

Currently, abbreviated procedures are being sought that will permit the testing of combinations of three or more drugs in relation to the drugs employed individually or in combinations of two. One such procedure is to test multiple combinations of drugs as compared with the drugs individually on optimal schedules. In this case one is considering the combination of drugs as though it were a new single agent and using it in whatever way is deemed to have the greatest likelihood of success. If the combination of three or more drugs is more effective than the most effective of the individual drugs on its optimal schedule, the multiple drug combination may then be explored further with comparison of combinations of two drugs etc. In this type of exploration the positive control may continue to change becoming, in each instance, the most effective therapy with the series of drugs being investigated.

IV. SUMMARY

In summary, it is undoubtedly true that as for the investigation of antitumor therapy with individual drugs so too with combinations of drugs the preclinical models may be highly useful in prediction for the clinic. At this point in time the clinical investigations with drug combinations are preceding the studies with experimental models and the challenge to the preclinical chemotherapist is to "catch up" with the clinic. But also, there is the obligation on the part of the clinical investigators to take into account the leads obtained in the preclinical investigations and also to provide a feedback of quantitative clinical information that can be used as a further guide to the preclinical investigations. The preclinical and clinical complementary association is necessary for the greatest progress with combination chemotherapy.

LIST OF COMPOUNDS

***N*-Acetylcysteine:** NSC-111180; CAS reg. No. 616-91-1; cysteine, *N*-acetyl-, L-

Actinomycin D: NSC-3053

Adriamycin: NSC-123127

Azaserine: NSC-742; CAS reg. No. 115-02-6; serine, diazoacetate (ester), L-

BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-

Bleomycin: NSC-125066

Bromochloromethotrexate: NSC-98579; glutamic acid, *N*-[3-bromo-5-chloro-4-[[(2,4-diamino-6-pteridinyl)-methyl]methylamino]benzoyl]-

Camptothecin: NSC-100880; CAS reg. No. 25387-67-1

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

***Cis*-diamminedichloroplatinum:** NSC-119875

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Cytosine arabinoside: NSC-63878; CAS reg. No. 69-74-9; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride

Daunorubicin: NSC-83142; CAS reg. No. 23541-50-6; daunomycin (NSC-82151)

Demecolcine: NSC-3096; colchicine, *N*-deacetyl-*N*-methyl-; Colcemid

Dichloromethotrexate: NSC-29630; glutamic acid, *N*-[3,5-dichloro-4-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8

5-FUDR: NSC-27640; 5-fluoro-2′-deoxyuridine

Guanazole: NSC-1895; 1,2,4-triazolidine, 3,5-diimino-

Hexamethylmelamine: NSC-13875

5-Hydroxypicolinaldehyde thiosemicarbazone: NSC-107392; CAS reg. No. 19494-89-4

Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1

ICRF–159: NSC-129943; 2,6-piperazinedione, 4,4′-propylenedi-, (±)-

Isophosphamide: NSC-109724; CAS reg. No. 3778-73-2; 1,3,2-oxazaphosphorine, 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-, 2-oxide

Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamino, 2,2′-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard

6-Mercaptopurine: NSC-755; CAS reg. No. 6112-76-1; purine-6-thiol, monohydrate; 6-MP

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Methyl-CCNU: NSC-95441; CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-

Methyl-GAG: NSC-32946; CAS reg. No. 24968-67-0; guanidine, 1,1′-[(methylethanediylidene)dinitrilo]di-, dihydrochloride, monohydrate

1-Methyl-1-nitrosourea: NSC-23909; CAS reg. No. 684-93-5

NSC-45388: CAS reg. No. 4342-03-4; imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno)-; DIC

NSC-60339: CAS reg. No. 70-09-7; terephthalanilide, 2-chloro-4′,4′′-di-2-imidazolin-2-yl-; TIC

NSC-82196: CAS reg. No. 5034-77-5; imidazole-4-carboxamide, 5-[3,3-bis(2-chloroethyl)-1-triazeno]-; BIC

6-Thioguanine: NSC-752; CAS reg. No. 1832-72-0; purine-6-thiol, 2-amino-

Vinblastine: NSC-49842; vincaleukoblastine, sulfate (1:1), monohydrate

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Remission Rates, Survival, and Prognostic Factors in Combination Chemotherapy for Bronchogenic Carcinoma [1,2]

Pierre Alberto [3,4]

SUMMARY

Studies on combination chemotherapy for bronchogenic carcinoma performed between 1965 and 1971 by the Swiss Group for Clinical Cancer Research are briefly reported. The best results were obtained with a simultaneous combination of methotrexate (20–25 mg/m², weekly), cyclophosphamide (60–80 mg/m², daily), procarbazine (80–90 mg/m², daily), and vincristine (1.0–1.2 mg/m², weekly). One hundred and twenty-five of the 153 patients treated according to this schedule were evaluable. The overall response rate was 48%. The tumor cell type and the extent of metastasis played an important role in the response to treatment. For patients with oat cell carcinoma, the response rate was 77% for locoregional tumors and 48% for disseminated tumors. The corresponding values for the patients with squamous cell carcinoma were 22% and 35%. The influence of therapeutic response on survival was limited to a prolongation of about 12 weeks for squamous cell carcinoma and 20 weeks for oat cell carcinoma.

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[1] Supported by the Swiss League Against Cancer and the Swiss National Fund for Scientific Research.

[2] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are listed in the List of Compounds at the end of the text.

[3] The author is the chairman of disseminated lung cancer studies, Swiss Group for Clinical Cancer Research. Participating members of the Swiss Group for Clinical Cancer Research are: *Drs. G. Nagel and H. J. Senn,* Oncohematology Unit, Department of Medicine, University of Basel; *Drs. K. Brunner, R. Sonntag, and P. Ryssel,* Oncology Station, Department of Medicine, University of Bern; *Drs. G. Martz and C. Sauter,* Hematology and Oncology Unit, Department of Medicine, University of Zürich; *Dr. P. Obrecht,* Oncology Unit, Department of Medicine, University of Freiburg i. B., Germany; *Drs. P. Maurice and P. Alberto,* Division of Oncohematology, Department of Medicine, University of Geneva.

[4] *Reprint requests to:* P. Alberto, MD, Division of Oncohematology, Department of Medicine, University of Geneva Medical School, Geneva Hospital, 1211 Geneva, Switzerland.

BACKGROUND AND METHODS

The first study of the Swiss Group for Clinical Cancer Research on combination chemotherapy for bronchogenic carcinoma was started in 1965. This was a phase II study with a combination of procarbazine and 5-fluorouracil (fig 1). The treatment consisted of a 4-week induction period with 250 mg of procarbazine given orally daily in combination with 5-fluorouracil starting with a loading dose of 36 mg/kg of body weight in 3 days. This was followed by six additional injections of 7 mg/kg given biweekly. At the end of the induction phase, the patients were divided into three groups according to the therapeutic result: treatment failures, "no change," and response (objective remissions). The "no change" group and the responding group were treated further with the same combination until relapse occurred. The results of this study were disappointing: the response

rate was less than 10% (table 1). These are unpublished data. In 1970 Gottlieb and Serpick (1) confirmed the poor value of the combination of procarbazine and 5-fluorouracil; using a different dosage, they obtained a response rate of only 1/12.

In 1968 we started a second study using a four-drug combination (methotrexate,[5] cyclophosphamide, procarbazine, and vincristine [6]). This was a phase III study comparing sequential treatment with simultaneous treatment (fig 2). The patients were randomized in two groups. The patients in one group were treated for 4 weeks with the combination of the four drugs; this treatment was followed by 4 additional weeks of treatment with three of the drugs (vincristine was omitted). Patients in the other group were treated for 2 weeks with each drug at full dosage, successively (8 weeks of treatment).

After this 8-week induction phase, the responding patients and the patients in the "no change" category were randomized in two groups for maintenance treatment: patients in one group received the same treatment as during the induction phase and patients in the other group received cyclophosphamide alone orally daily.

The results of the induction phase are shown in table 2. The response rate for the simultaneous regimen was significantly superior to that for the sequential regimen (51% and 21%, respectively). Under these conditions, the sequential arm was withdrawn and the simultaneous regimen was continued without randomization. Table 3 shows the results of the induction phase for this additional nonrandomized series. The response rate for the nonrandomized series was not significantly different from that of the 1968 randomized study.

In 1971 we decided to study the value of a sequence of two drugs, starting with a cell-cycle-stage-nonsensitive (CCS-NS) agent, followed by a cell-cycle-stage-sensitive (CCS-S) agent, according to Schabel's hypothesis (2). This type of combination was advocated by Selawry in a Combined Clinical Staff Conference of the National Cancer Institute in 1970 (3). We chose our four-drug combination as a reference arm and the patients were allocated to either of the regimens by randomization. Figure 3 shows the dosage schedule of this study. As far as induction was concerned, the four-drug combination appeared to be superior, giving a response rate of 50%, which, again, was quite comparable to our previous results (table 4).

The purpose of this communication is not to discuss each of these studies, but to analyze the main prognostic factors in combination chemotherapy for bronchogenic carcinoma in the light of our experience with a four-drug combination applied between 1968 and 1971 in three successive studies with reproducible results.

RESULTS

Remission Rates

The overall response rate in the cumulative series of 153 cases is shown in table 5. Forty-eight percent of 125 evaluable patients responded. One of the most important prognostic factors in the chemotherapy for bronchogenic carcinoma seems to be the tumor cell type. If the response rates are stratified according to this criterion (as shown in table 6), it becomes apparent that the oat cell carcinomas are much more responsive than the squamous cell carcinomas (response rates of 62% and 28%, respectively, for patients in these series). For the anaplastic medium-sized cell and large cell tumors, the response rate is 50%. Although the number of observations of patients with adenocarcinoma is insufficient for good assessment, adenocarcinoma seems to be responsive as well. This difference in responsiveness between oat cell and squamous cell carcinomas does not seem to be specific for this particular combination regimen. In a smaller unpublished study of combination treatment with CCNU, adriamycin, and hydroxyurea, we observed objective remissions in three of five cases of oat cell carcinoma, one of nine cases of squamous

[5] Methotrexate was supplied by Dr. H. Raths, Opopharma A. G., Zürich, representative of Lederle Laboratories Division, American Cyanamid Company, Pearl River, NY.

[6] Vincristine was supplied by Dr. L. Forgacs, Chief of the Medical Department, G. Richter, Budapest, Hungary.

cell carcinoma, and three of five cases of anaplastic carcinoma.

Another important factor is the extent of metastasis. If the remission rate for patients with locoregional dissemination only is compared with that of patients with distant metastases outside the thorax (as in table 7), different results for patients with oat cell tumors and patients with squamous cell tumors will be noted. In patients with oat cell tumors, the remission rate is better when there is only locoregional spread than when there is disseminated disease (remission rates of 77% and 48%, respectively). In contrast, the extent of the metastatic process does not seem to play an appreciable role for squamous cell carcinoma (remission rates of 22% and 35%, respectively).

Survival

Figures 4–10 illustrate the influence of the obtained remissions on survival. These are simple actuarial curves, calculated for survival intervals of 4 weeks, starting at the beginning of the induction treatment. For each curve, the total number of evaluable observations on Day 1, the number of tumor-related deaths and surviving patients at the time of assessment, and the number of patients (either surviving or dead) lost to followup for causes unrelated to the tumor are given.

Figures 4–6 show the survival curves of the patients with oat cell carcinoma who responded and those who failed to respond for the simultaneous treatment series of the randomized study (Protocol No. 15/68A) and for the additional monrandomized simultaneous treatment series (Protocol No. 15/70), separately or combined. The curves are comparable and show a shift to the right of the curve for responding patients corresponding to about 20 weeks. Figures 7–9 give the corresponding curves for the patients with squamous cell tumors. Here, the shift to the right of the curve for responding patients is less pronounced (not exceeding 12 weeks). Figure 10, a composite of figures 4–9, demonstrates the good reproducibility of Protocols Nos. 15/68A and 15/70, and facilitates the comparison of the failures and responses of patients in both histologic groups. This figure suggests that in the oat cell tumor group the survival curve of the responding patients differs from that of the treatment failures not only by the shift to the right, but also by the flattening of the slope. In the squamous cell tumor group, the slopes of the curves for the responding patients and the treatment failures do not seem to be different.

Another important point is the behavior of the "no change" category for both cell type groups. Figures 11 and 12 show that in the oat cell group the "no change" curve has an intermediate position between that for the treatment failures and the responses, whereas in the squamous cell group the "no change" curve corresponds to a better survival than does the curve for the responding patients. This suggests that the therapeutic significance of the absence of progression of disease is quite different according to cell type. In the oat cell tumor series, the "no change" response corresponds to an antitumor effect of insufficient magnitude. In the squamous cell tumor series, the "no change" category probably represents a particular group of slowly progressing tumors in which the therapeutic effect can hardly be evaluated.

CONCLUSIONS

Our observations concerning the response rate and the influence on survival of treatment with a simultaneous combination of methotrexate, procarbazine, cyclophosphamide, and vincristine lead us to the following conclusions:

(*a*) Combination chemotherapy for bronchogenic carcinoma is effective in inducing remissions. The responsiveness of the tumor is highly dependent on the cell type. This point can generate much confusion, since the histologic typing of bronchogenic carcinoma leads to many disagreements among pathologists. Nevertheless, our results suggest clearly that the oat cell tumors respond better than the squamous cell tumors. This difference in behavior corresponds well to the different radiosensitivities of the same tumor types. The adenocarcinomas,

in contrast, seem to be more sensitive to combination chemotherapy than to radiotherapy.

(*b*) The induced remissions may dramatically improve the symptoms of the disease and the performance index of the patient. This is perhaps the most important advantage of combination chemotherapy over single-drug therapy for bronchogenic carcinoma.

(*c*) Despite these promising results in the induction of objective remissions, the effect of the treatment on survival is disappointing. Although we did not compare the duration of unmaintained and maintained remissions, our results suggest that the maintenance treatments, as applied in our studies, have little, if any, value.

In other fields of tumor chemotherapy, where maintenance treatment has profoundly altered the survival of the patients (eg, acute leukemia of childhood [4]), this effect is demonstrable by a flattening of the survival curve, which tends to level off after a given period of time. In our studies, however, the slope of the survival curve is hardly modified. This suggests that the value of combination chemotherapy for bronchogenic carcinoma, as applied in our studies, is probably rapidly compromised by the appearance of drug resistance. If this hypothesis is correct, it suggests that the tumor cell fraction primarily resistant to the combination treatment is relatively high, even when the reduction of the size of the tumor is impressive.

It could be postulated that maximum benefit could be obtained from combination chemotherapy by taking advantage of the known relationship between drug sensitivity and tumor growth kinetics. In this respect, the theoretical approach proposed by Schabel (2) (fig 13) could be carried out in clinical chemotherapy for bronchogenic carcinoma since both CCS-S agents (methotrexate, vincristine, hydroxyurea) and CCS-NS agents (alkylating agents, procarbazine, nitrosoureas, adriamycin) have proved to be of some value against this type of tumor. However, in order for the theoretical mechanism proposed by Schabel to be effective, the first application of CCS-NS agents must be able to achieve a tumor cell kill in the order of magnitude of 2 $\log_{10}$.

It is very probable that none of the CCS-NS agents potentially active against bronchogenic carcinoma could induce such an important reduction of the tumor cell population when used alone; however, this reduction could possibly be achieved by a combination of CCS-NS agents (eg, cyclophosphamide plus procarbazine plus CCNU plus adriamycin). The CCS-S phase of treatment could, for the same reason, consist of a combination of CCS-S agents (eg, methotrexate plus vincristine plus hydroxyurea). The Swiss Group for Clinical Cancer Research is now engaged in a study based on this hypothesis.

LIST OF COMPOUNDS

Adriamycin: NSC-123127

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate

Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-

Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-α-(2-methylhydrazino)-, monohydrochloride

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

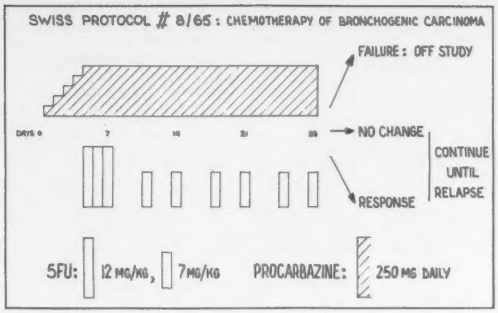


FIGURE 1.—Swiss Group for Clinical Cancer Research: phase II study of combination chemotherapy with 5-FU and procarbazine.

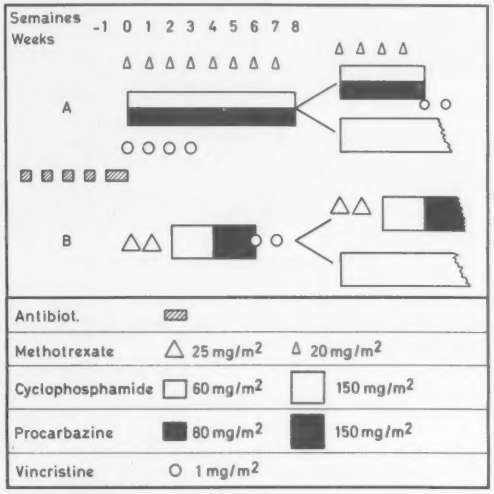


FIGURE 2.—Swiss Group for Clinical Cancer Research: phase III study of combination chemotherapy for bronchogenic carcinoma with methotrexate, cyclophosphamide, procarbazine, and vincristine.

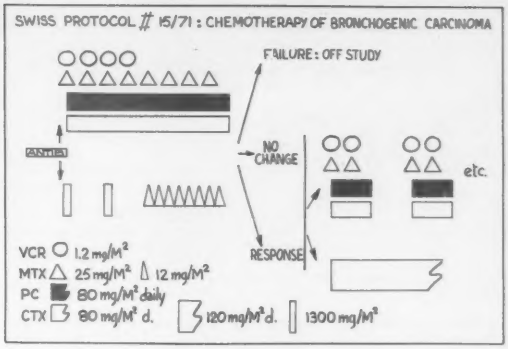


FIGURE 3.—Combination chemotherapy with vincristine (VCR), methotrexate (MTX), procarbazine (PC), and cyclophosphamide (CTX) compared to sequential treatment with a CCS-NS agent (CTX) and a CCS-S agent (MTX).

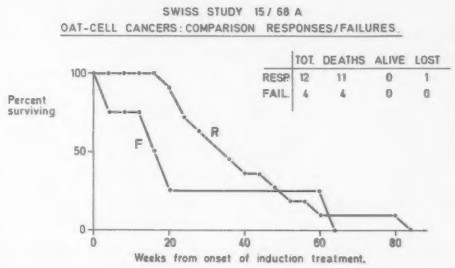


FIGURE 4.—Survival curves for patients with oat cell carcinoma treated with combination chemotherapy (randomized study). F = treatment failures; R = responding patients.

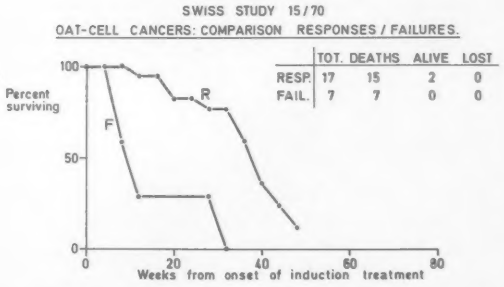


FIGURE 5.—Survival curves for patients with oat cell carcinoma treated with combination chemotherapy (additional nonrandomized series). F = treatment failures; R = responding patients.

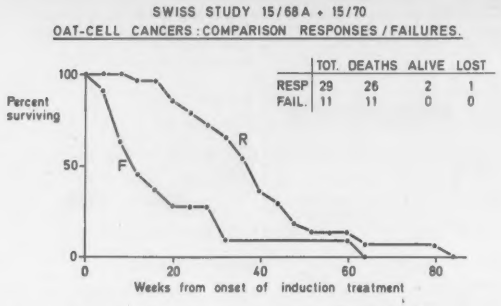


FIGURE 6.—Survival curves for patients with oat cell carcinoma treated with combination chemotherapy (combined series). F = treatment failures; R = responding patients.

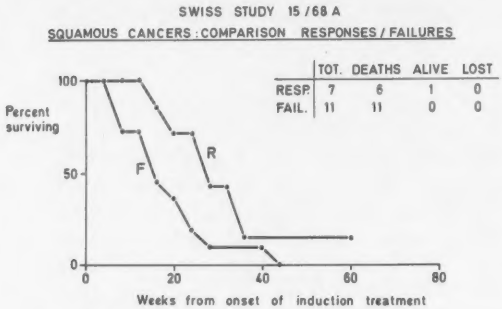


FIGURE 7.—Survival curves for patients with squamous cell carcinoma treated with combination chemotherapy (randomized study). F = treatment failures; R = responding patients.

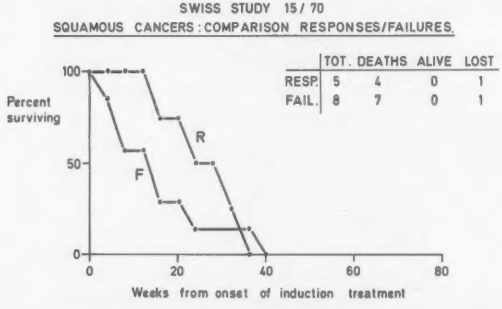


FIGURE 8.—Survival curves for patients with squamous cell carcinoma treated with combination chemotherapy (additional nonrandomized series). F = treatment failures; R = responding patients.

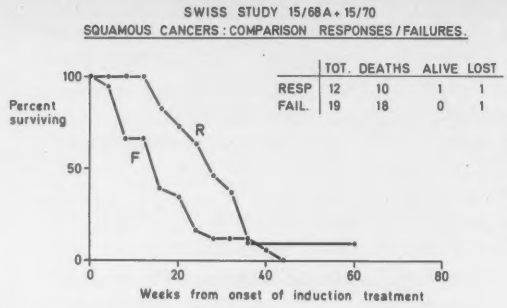


FIGURE 9.—Survival curves for patients with squamous cell carcinoma treated with combination chemotherapy (combined series). F = treatment failures; R = responding patients.

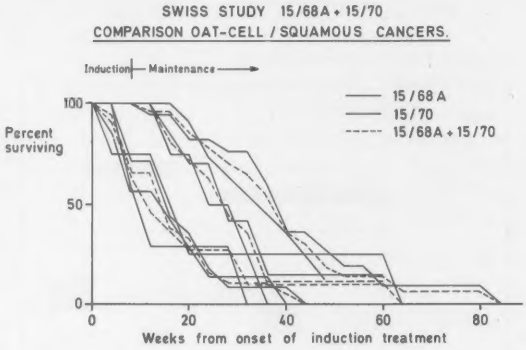


FIGURE 10.—Survival curves for patients with oat cell carcinoma or squamous cell carcinoma treated with combination chemotherapy.

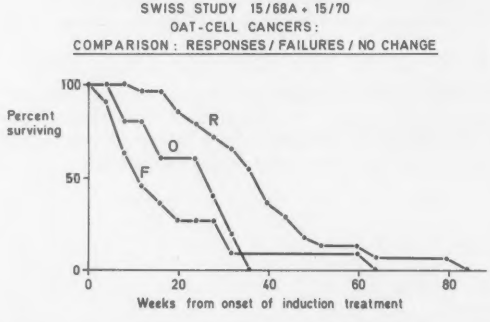


FIGURE 11.—Survival curves for patients with oat cell carcinoma. F = treatment failures; O = "no change"; R = responses.

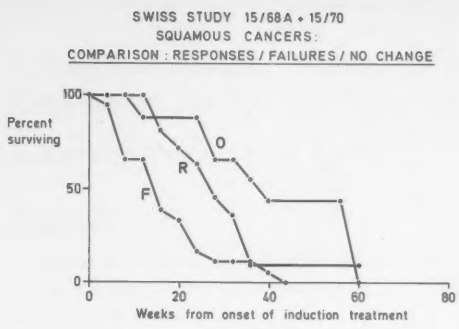
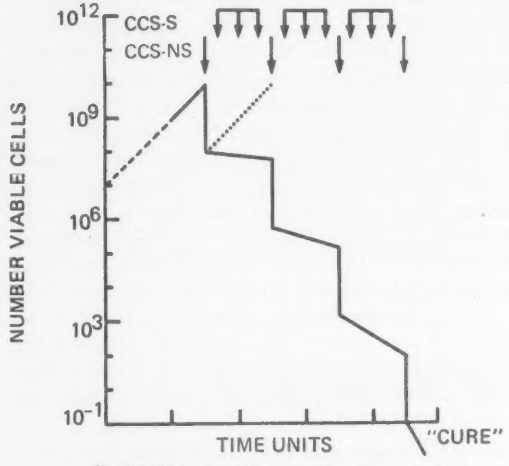


FIGURE 12.—Survival curves for patients with squamous cell carcinoma. F = treatment failures; O = "no change"; R = responses.



Combination chemotherapy of solid tumors
CCS-S = cell cycle stage, sensitive; CCS-NS = cell cycle stage, nonsensitive.

FIGURE 13.—Combination chemotherapy for solid tumors (from Selawry in Carbone et al [3]).

TABLE 1.—Swiss Group for Clinical Cancer Research Protocol No. 8/65: phase II study of combination chemotherapy for bronchogenic carcinoma*

Treatment	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Simultaneous combination: procarbazine + 5-FU	33	31	2 (6)

**See* text for description of dose and treatment schedule.

TABLE 2.—Swiss Group for Clinical Cancer Research Protocol No. 15/68: phase III study of combination chemotherapy for bronchogenic carcinoma*

Treatment	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Simultaneous combination: methotrexate + cyclophosphamide + vincristine + procarbazine	64	49	25 (51)
Sequential combination: methotrexate + cyclophosphamide + vincristine + procarbazine	54	43	9 (21)

**See* text for description of doses and treatment schedules.

TABLE 3.—Swiss Group for Clinical Cancer Research Protocol No. 15/70: study of combination chemotherapy for bronchogenic carcinoma (continuation of simultaneous treatment regimen, protocol No. 15/68)*

Treatment	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Simultaneous combination: methotrexate + cyclophosphamide + vincristine + procarbazine	67	60	27 (45)

**See* text for description of dose and treatment schedule.

TABLE 4.—Swiss Group for Clinical Cancer Research Protocol No. 15/71A: chemotherapy for bronchogenic carcinoma*

Treatment	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Simultaneous combination: methotrexate + cyclophosphamide + vincristine + procarbazine	22	16	8 (50)
Sequential combination: cyclophosphamide + methotrexate	30	24	6 (25)

**See* text for description of doses and treatment schedules.

TABLE 5.—Swiss Group for Clinical Cancer Research Protocols Nos. 15/68A, 15/70, and 15/71A: chemotherapy for bronchogenic carcinoma*

Treatment	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Simultaneous combination: methotrexate + cyclophosphamide + vincristine + procarbazine	153	125	60 (48)

*Overall response for the cumulative series.

TABLE 6.—Chemotherapy for bronchogenic carcinoma with a simultaneous combination of methotrexate + cyclophosphamide + vincristine + procarbazine

Cell type	Total No. of patients treated	No. of evaluable patients	No. of responses (%)
Oat cell	59	53	33 (62)
Squamous cell	58	46	13 (28)
Anaplastic	19	16	8 (50)
Adenocarcinoma	7	7	5
Alveolar	1	0	0
Nonspecific	9	3	1
Total	153	125	60 (48)

TABLE 7.—Chemotherapy for bronchogenic carcinoma with a simultaneous combination of methotrexate + cyclophosphamide + vincristine + procarbazine

	No. of responding patients/No. of evaluable patients (%)		
Cell type	Locoregional disease	Disseminated disease	Total
Oat cell	20/26 (77%)	13/27 (48%)	33/53 (62%)
Squamous cell	5/23 (22%)	8/23 (35%)	13/46 (28%)

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Chemotherapeutic Studies in Bronchogenic Carcinoma by the Austrian Study Group

K. Karrer,[1] N. Pridun,[2] and E. Zwintz [2]

SUMMARY

Since the autumn of 1969, studies of surgical adjuvant chemotherapy and of chemotherapy alone in bronchogenic carcinoma have been undertaken at the Hospital Wien-Lainz. Preliminary data from 55 radically operated patients, 27 randomized control patients, and 71 inoperable patients receiving chemotherapy only are presented. Chemotherapy was carried out as follows: 1–2 weeks after surgery the first intravenous infusion of 500 ml of 5% Laevulose including 12 mg/kg of cyclophosphamide, 12 mg/kg of 5-fluorouracil, 0.5 mg/kg of methotrexate, and 0.1 mg/kg of vinblastine was administered. The protocol requires the administration of 13 such infusions within 3 years after the operation. In general, the treatment, which consisted of a total of 500 infusions administered to 55 radically operated patients, was well tolerated and caused only minor side effects. The survival rate of the treated group of patients (calculated by the life-table method) appears promising compared with the survival rate of the randomized and historical control patients. The subdivision of patients into Feinstein categories shows a great variation, indicating the importance of the clinical parameters in influencing the prognosis. Based on a total of 466 chemotherapeutic infusions in 71 patients with inoperable bronchogenic carcinoma, it can be stated that the treatment used was surprisingly well tolerated considering the advanced stage of disease and therefore the poorer general condition of these patients. To confirm our results, a total of 300 predominantly inoperable patients were treated by the originally proposed five-drug regimen in nine other cooperative hospitals. These preliminary results justify the continuation of these clinical trials in a larger cooperative study group.

[Cancer Chemother Rep Part 3, vol 4:207–213, 1973]

Since 1955, studies of systemic chemotherapy as an adjuvant to radical surgical treatment of bronchogenic carcinoma have been conducted by the Viennese Working Group. Five studies using six different dose schedules in 678 patients have been undertaken. The rationale for this program of high-dose intermittent long-term adjuvant polychemotherapy is based on the following considerations:

1. The results achieved so far in our trials support the concept that intermittent chemotherapy is preferable to continuous chemotherapy. This preference might be based on a better balance between the

[1] Institute for Cancer Research of the University of Vienna, Austria.

[2] I. Surgical Department of the Hospital Wien-Lainz, Vienna, Austria.

desired tumor-inhibitory effect and undesirable immunosuppression.

2. The drug dose must be as high as possible for maximal cell kill of small groups of tumor cells (micrometastases) in the organism.
3. Chemotherapy should be started as early as possible, because it has been shown in experiments that the effect of chemotherapy is greatest when the metastases are small.
4. At present, the cytostatic drugs available are not able to destroy all tumor cells in the organism completely, and even with the highest doses only a certain proportion of tumor cells can be eliminated per drug dose; the therapy should therefore be extended over a longer period of time.

PATIENTS

Since the autumn of 1969, studies on surgical adjuvant chemotherapy of bronchogenic carcinoma as well as chemotherapy alone in patients with inoperable tumors have been undertaken at the Hospital Wien-Lainz. The data from this preliminary evaluation (as of September 1, 1972) are presented for discussion.

Fifty-five patients who had received radical surgery and 71 inoperable patients were treated with polychemotherapy; an additional 27 patients who had received radical surgery were randomly allocated as controls.

In figure 1 the 55 radically operated patients are subdivided according to stage (TNM classification, categories I–IV), Feinstein classifications (I–V), and histologic type of tumor. The percentage of asymptomatic patients (Feinstein's category I) shown in figure 1 is quite similar to that in the original paper by Feinstein (1), indicating that no particularly successful means of early diagnosis was present, in contrast to Berndt's report (2). The 32 patients with squamous cell carcinoma and the five patients with oat cell carcinoma show little correlation between anatomic and symptomatic staging, except for the relatively higher incidence of oat cell carcinoma in TNM stages III and IV. A similar pattern occurs in the 27 randomized control patients who received radical surgery only at the same time, in the same department, and by the same method and surgeon (fig 2).

The age distribution of all patients who received radical surgical treatment is given in table 1. The breakdown of TNM stages is shown in figure 3, and Feinstein groups are classified according to the definitions published in 1964 (1).

The number of patients who received chemotherapy only is plotted in figure 4 according to the TNM and Feinstein classifications and the histologic tumor type. As can be seen in figure 4, there is a relatively high incidence of squamous cell carcinoma in TNM stage IV M_0 compared with the incidence in the group of stage IV M_1 patients (five of 25). In contrast, the distribution of oat cell carcinoma shows a higher incidence in the stage IV M_1 group (six of 25) than in the stage IV M_0 group (three of 35). There is no particular distribution of the histologic types among the Feinstein categories.

The age distribution of the patients receiving chemotherapy only is given in table 2.

TABLE 1.—Age distribution of patients with bronchogenic carcinoma who received radical surgical treatment

Treatment	Sex	No. of patients	Age groups (yrs)							
			36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75
Surgery + chemotherapy	M	46	1	—	6	2	9	17	11	—
	F	9	—	—	1	—	4	3	—	1
Total		55	1	—	7	2	13	20	11	1
Surgery only	M	24	—	1	5	2	6	5	4	1
	F	3	—	—	—	1	1	—	1	—
Total		27	—	1	5	3	7	5	5	1

TABLE 2.—Age distribution of patients receiving chemotherapy only

Age group	Sex		No. of patients
	M	F	
31–35	1	1	2
36–40	3	1	4
41–45	2	—	2
46–50	6	4	10
51–55	4	—	4
56–60	13	3	16
61–65	13	1	14
66–70	15	1	16
71–75	2	—	2
76–80	1	—	1
Total	60	11	71

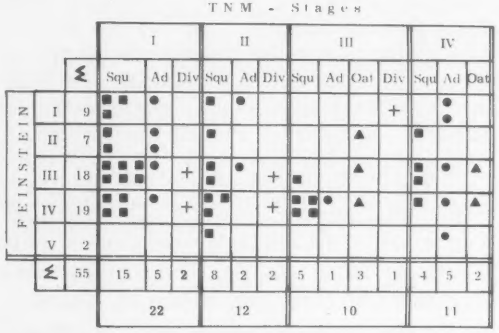

FIGURE 1.—Staging (TNM stages I–IV) of patients receiving surgical adjuvant chemotherapy. Squ = squamous cell carcinoma; Ad = adenocarcinoma; Oat = oat cell carcinoma; Div = other cell types.

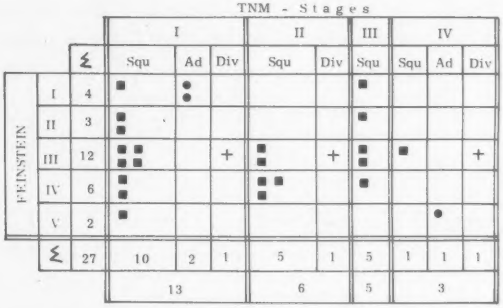

FIGURE 2.—Staging (TNM stages I–IV) of patients receiving radical surgical treatment only. *See* figure 1 for definitions of cell types.

TNM Stages

Stage I = $T_1 N_a$, $T_2 N_a$ — M_0

Stage II = $T_1 N_b$, $T_2 N_b$ — M_0

Stage III = $T_1 N_c$, $T_2 N_c$, $T_3 N_{a,b}$ — M_0

Stage IV = $T_3 N_c$, $T_4 N_{a,b,c}$ — M_0; $T_x N_x$ — M_1

FIGURE 3.—Breakdown of TNM stages.

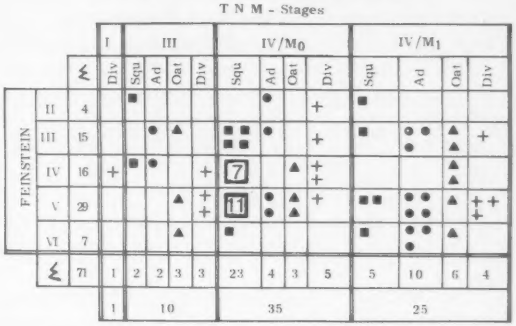

FIGURE 4.—Staging of patients (TNM stages I, III, and IV) with inoperable bronchogenic carcinoma. *See* figure 1 for definitions of cell types.

We were not able to estimate the growth rates and doubling times in these patients by Israel's method (3).

MATERIAL AND METHODS

Chemotherapy was carried out as follows: 1–2 weeks after surgery the first intravenous infusion of 500 ml of 5% Laevulose including 12 mg/kg of cyclophosphamide, 12 mg/kg of 5-FU, 0.5 mg/kg of methotrexate, and 0.1 mg/kg of vinblastine was administered.[3] After in-

[3] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8; 5-FU.

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

Vinblastine: NSC-49842; CAS reg. No. 6449-03-2; vincaleukoblastine, sulfate (1:1), monohydrate.

tervals of 6 days the infusions were repeated a second and third time. The protocol requires the administration of 13 such infusions within 3 years after operation.

The first three infusions of this chemotherapy were administered in the hospital within the postoperative period and the subsequent infusions were administered in the outpatient department. General practitioners are informed of the treatment procedures by an explanatory letter and are asked to give psychological help, advice, and care to the patient.

During the treatment period, leukocytes were counted twice a week. If the white blood cell counts (wbc) before the next treatment were less than 4000 cells/mm^3 and the platelet counts were less than 100,000 platelets/mm^3, the 6–8-week period without treatment was prolonged.

Beginning in the spring of 1971, the radically operated patients were randomly divided so that half received chemotherapy as outlined above while the other half received only the same medical care given after surgery without cytostatic treatment. These patients were called into the hospital for examination at the same time as those treated with cytostatic agents.

RESULTS

A total of 500 infusions (average, nine infusions per patient) were administered to 55 of the patients who received radical surgical treatment. In general, the treatment was well tolerated and caused only minor side effects, such as vomiting and nausea for 1–2 days. Loss of hair and diarrhea were rare. No patient required hospitalization, and many patients interrupted their work only for the 1 day of infusion. Particularly important is the fact that the rate of leukopenia noted in this study was lower than the rate noted during a previous study using high-dose single-drug therapy. Table 3 demonstrates that only 12 of 55 patients had leukopenia with wbc less than 2000 cells/mm^3. Recovery from leukopenia occurred after administration of cortisone and blood transfusions, and few patients received antibiotics and gamma globulins prophylactically.

The survival rates are calculated by the usual life-table method. The comparison of the survival in the treated patients with the survival in the randomized and historical control patients is demonstrated in figure 5. This figure represents all patients who had tumors in TNM stage I (small tumors, T_1 or T_2) but did not have tumor cells in the lymph nodes as proved by routine histologic examination. The number of patients upon which the calculation is based is indicated at the 12- and 20-month points of each life-table curve. If the 22 stage I patients receiving combined treatment are subdivided into the Feinstein categories, the comparison of the life-table curves shows quite a variable range (fig 6). This indicates the importance of these parameters in determining the prognosis and subsequently in evaluating the life-tables.

Some of the patients received only the initial infusions and subsequent chemotherapy was discontinued for various nonmedical reasons (mainly because the patients lived outside Vienna in the country). This has also been taken into account in evaluating these results.

TABLE 3.—Effect of high-dose chemotherapy on peripheral leukocytes in patients with bronchogenic carcinoma after radical operation

No. of patients	Infusions		Leukocytes not below (cells/mm^3)
	No. (range)	Average	
43	1–30	8.2	2000
7	5–23	12.8	1500
4	3–23	12.5	1000
1	6	6.0	950
55	500	9	

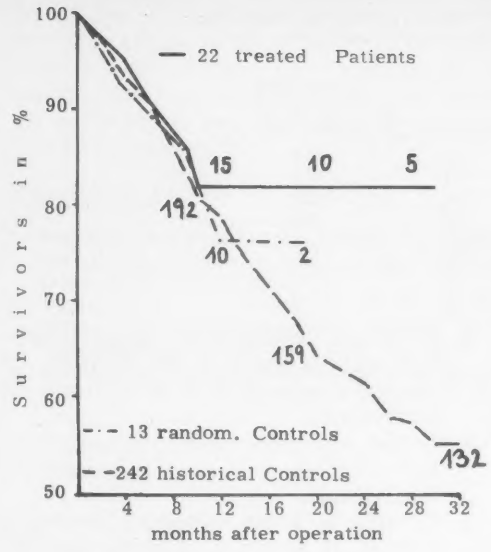

FIGURE 5.—Survival of stage I patients receiving surgical adjuvant chemotherapy compared with survival of randomized and historical control patients.

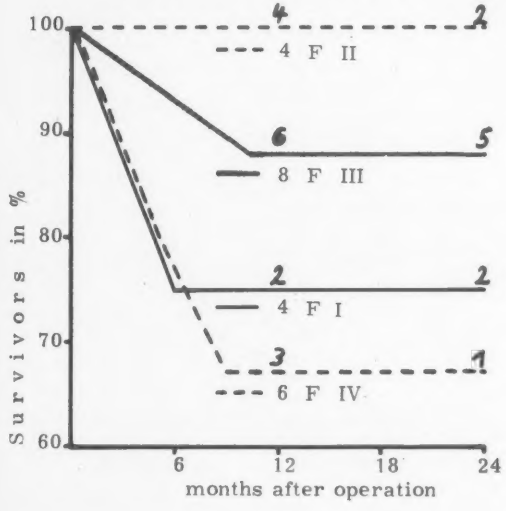

FIGURE 6.—Survival of TNM stage I patients receiving surgical adjuvant chemotherapy subdivided by Feinstein (F) categories.

Similar intermittent high-dose polychemotherapy was administered to patients with inoperable bronchogenic carcinoma. The dose schedule used is shown in figure 7. Based on the total of 466 high-dose chemotherapy infusions given to 71 patients with inoperable bronchial carcinoma it can be stated that the treatment was surprisingly well tolerated considering the advanced stage of disease and therefore the poorer general condition of these patients. This is also confirmed by the relatively low incidence of leukopenia as demonstrated in table 4. The life-table curves of the inoperable patients grouped into TNM and Feinstein classifications are given in figure 8. As mentioned before, the division of these patients into Feinstein categories demonstrates important prognostic differences.

DISCUSSION

Our cooperative study group for chemotherapy of bronchogenic carcinoma has since increased and a total of about 300 predominantly inoperable patients were treated by the same method, using the originally proposed five-drug chemotherapy consisting of 12 mg/kg of cyclophosphamide, 12 mg/kg of 5-FU, 0.5 mg/kg of methotrexate, 0.1 mg/kg of vinblastine, and 0.1 mg/kg of mitomycin C[4] in nine other hospitals in Austria, East Germany, West Germany, and Belgium. In general, the same encouraging observations have been seen in all these other hospitals. Therefore, we can conclude from this preliminary evaluation that:

1. The treatment used is generally well tolerated and can be effectively administered under certain conditions.
2. Leukopenia and other side effects are within an acceptable range.
3. The survival rates justify the continuation of these trials in increased numbers of particular hospitals in a larger cooperative study group.

Because of the relatively small number of patients treated in each group, the following conclusions must be confirmed by further studies in larger cooperative groups:

1. Short-term treatment was ineffective.

[4] Mitomycin C: NSC-26980; CAS reg. No. 50-07-7.

TABLE 4.—Effect of high-dose chemotherapy on peripheral leukocytes in patients with inoperable bronchogenic carcinoma

No. of patients	Infusions		Leukocytes not below (cells/mm³)
	No. (range)	Average	
53	1–25	7.1	2000
9	1–15	4.8	1500
4	2–9	5.0	1000
5	2–8	4.8	600
71	466	6.5	

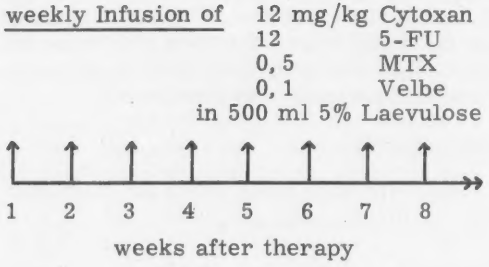

FIGURE 7.—Dose schedule for intermittent high-dose chemotherapy in patients with inoperable bronchogenic carcinoma (Velbe = vinblastine).

2. Long-term treatment with eight intermittent courses given within 2 years of surgical treatment showed an increased survival rate.
3. Longer treatment, using 13 courses within 3 years, showed a further increase in survival rate.
4. Patients in whom leukopenia developed because of adjuvant chemotherapy exhibited an increased survival rate compared with nonleukopenic patients treated with the same dose schedules.
5. A pilot study using a high pulse dose of cyclophosphamide (infusions of 25–30 mg/kg) gave encouraging results (4).

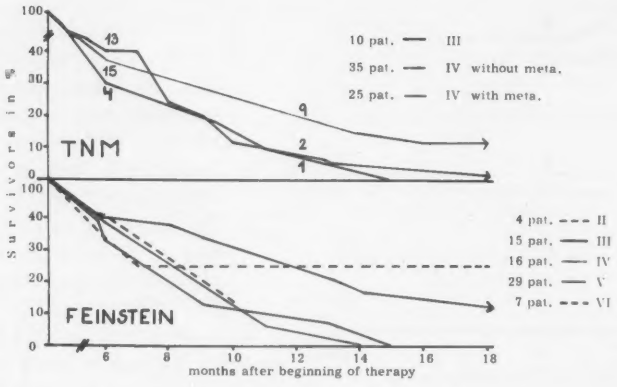

FIGURE 8.—Survival of inoperable patients grouped into TNM and Feinstein classifications.

Considering the results of experimental studies on appropriate animal model systems (5) and other clinical results reported in the literature, a new program for chemotherapy of bronchogenic carcinoma as an adjuvant to radical surgery (6) and for inoperable patients (7) was suggested.

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Initial Therapeutic Trial of New Drugs in Lung Cancer

Oleg S. Selawry [1]

SUMMARY

Current phase II initial therapeutic trials show marked differences in reported objective response rates in patients with lung cancer. A master protocol is proposed, based on recommendations made at the International Workshop for Therapy of Lung Cancer. Prominent features of the protocol include stratification of patients by cell type, stage of disease, prior treatment, and immunologic status and cell types, and random allocation to a crossover design using cyclophosphamide as the standard agent.

[Cancer Chemother Rep Part 3, vol 4:215–225, 1973]

The importance of the initial therapeutic trial of a new drug cannot be overemphasized. It takes years to pass the following preclinical phases of drug development: recognition of antineoplastic activity in representative animal tumors; schedule dependency; formulation; and preclinical toxicology. Safely tolerated dose levels and dose schedules are determined during the initial clinical trial—the "phase I" of clinical exploration. After this, the new drug enters phase II, the crucial test of antineoplastic activity against human tumors. Against this background it is the foremost task of the initial therapeutic trial to avoid false negative results with reasonable certainty.

It is common practice to study each new drug in at least 14 patients with a given tumor, because a study with 14 consecutive treatment failures permits rejection of a response rate of 20% with a rejection error of 5% (1). Some authors prefer to treat at least 19 patients, because 19 consecutive treatment failures will exclude a 15% response rate with a rejection error of 5%.

The statistical reasoning is impeccable. The salvation does not lie, however, in mere numbers. This is illustrated in table 1, where response rates in different trials of mechlorethamine [2] varied between 0 and 68%. Response in none of 36 patients (2) would have excluded a possible response rate of 9% with a rejection error of 5% (1). Thus, an overall response rate of 36% in 1266 patients reported in the literature (10) would have been missed.

Classification of the authors into optimists and pessimists is too simplistic an explanation for the wide variation of response rates and

[1] National Cancer Institute-Veterans' Administration Medical Oncology Branch, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

[2] Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard.

TABLE 1.—Objective response of lung cancer to mechlorethamine

No. of patients		Percent responding	Reference No.
Entered	Responding		
36	0	0	2
26	1	4	3
58	6	10	4
61	12	20	5
43	13	30	6
21	8	38	7
41	19	46	8
54	37	68	9

does an injustice to their professional competence. Instead, the wide variations of response rates depend, among other things, on factors such as cell type and stage of the tumor, performance and immunologic status of the host, prior therapy, intensity and duration of the present treatment, and criteria for evaluation of objective response. It is suggested, therefore, to log these factors for each patient, to present them in publications of phase II studies, and to pinpoint their prognostic significance in larger studies. Moreover, it might be desirable to use study designs which permit inclusion of "good risk patients" into phase II trials, without denying them the benefits of chemotherapy of established value. Such study designs have an added advantage: they permit comparison of the new drug with a "standard treatment" as a common denominator for response rates. Information on cross-resistance will become available where crossover designs are used. Thus, crucial baseline information is gained for larger and more sophisticated comparative clinical trials.

The present paper contains proposals for a master protocol for phase II initial therapeutic trials of new drugs in patients with bronchogenic carcinoma. The elements of the proposed study design are in no way original. They were first presented at staff meetings of the National Cancer Institute in 1970. Numerous discussions, last but not least at the International Workshop for Therapy of Lung Cancer, led to the present recommendations. These recommendations form an admittedly arbitrary but mutually acceptable basis for study design as agreed upon at the Workshop; they represent one of several options and should be improved or reconsidered at appropriate time intervals. The credit for the concepts of this paper goes foremost to the following colleagues: V.I. Astrachan (Moscow), G. Bonadonna (Milan), K. Brunner (Bern), P. Carbone (NCI) D. Carr (Rochester, Minn), S. Carter (NCI), L. Israel (Paris), K. Karrer (Vienna), Y. Kenis (Brussels), C. Moertel (Rochester, Minn), C. Mountain (Houston), N. Perevodchikova and A. Pirogov (Moscow), M. Schneiderman (NCI), M. Zelen (Buffalo), C.G. Zubrod (NCI), and to my past and present co-workers, H. Hansen, F. Muggia, M. Cohen, P. Creaven, and S. Newman.

The *front sheet* of the Master Protocol (appendix 1) is self-explanatory. It contains the title of the study, an index, and a short outline of the study plan.

The *Introduction* includes an explanation of reasons and rationale for the present study. Detailed background information is best explained in a separate section at the end of the protocol. This permits the reader to proceed to instructions related to patient selection and treatment.

The *Objectives* of the study are directed toward determination of the effect of a given drug (or a new combination of drugs) on one or more of the following:

1. Objective tumor regression: incidence, extent, onset, and duration of response of the primary tumor and of major sites of metastases.
2. Relation of response to survival.
3. Relation of response to clinical benefit such as improved performance, weight gain, and pain relief.

It is desirable to include a statement of the estimated number of patients needed to recognize (or exclude) a given response rate with a given probability (1). Fourteen patients per major cell type of lung cancer represents a minimum for evaluation of tumor regression (*see* above).

Survival as the sole criterion of response (without measurement of tumor size) is a relatively insensitive, time-consuming, and expensive method for determination of response in initial therapeutic trials. Concomitant control groups are imperative, because median survival of successive, staged, placebo-treated control groups, treated by members of a cooperative study group, varied by more than 50% (12–14). Hence, approximately 20 patients would be needed in each arm of a random allocation study in order to detect a 100% difference in median survival. The number would increase to approximately 50 patients for detection of a 50% increase in median survival. Corresponding figures for a 20% increase in median survival would be in the

neighborhood of 230 patients; and indeed, only two of more than 12 agents studied showed superiority over placebo (12). Longer survival of responders might be obscured by shortened survival of nonresponders who are exposed to potentially toxic drugs in the presence of progressive disease.

The *Study Design* permits options: the study can be uncontrolled, with inclusion of up to 14 evaluable patients per major cell type and progression to a comparative clinical trial, when antineoplastic activity is recognized. This approach requires admission of patients with a good chance for response.

We prefer a controlled approach, with built-in controls against an unfavorable patient selection. Patients who qualify are allocated at random to one of two treatments: standard treatment (*A*) or experimental treatment (*B*). Randomization can be stratified by factors which might strongly modify response (cell type, stage of disease, prior treatment, etc). Treatment in both regimens is started at a pre-fixed dose level and dose schedule. The dose level is then adjusted to individual tolerance (moderate, reversible toxicity). Treatment is continued until progression of disease is noted. This permits cross-correlation between extent and duration of response.

As progression of disease is noted, patients are crossed over: those progressing on drug A will now receive drug B and vice versa. Thus, twice as many patients will be needed for the controlled initial clinical trial as for an uncontrolled trial. The crossover design will indicate response rates after prior treatment and might give clues for cross-resistance. A fixed sequence of treatments will also facilitate the use of survival as a parameter for response.

The participants of the Workshop chose cyclophosphamide,[3] 1000 mg/m²/dose given intravenously q 3 wks as the standard treatment for all cell types of lung cancer, to be replaced by other standard agents as they prove superior to cyclophosphamide in controlled clinical trials.

[3] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

PATIENT SELECTION

Each patient must qualify for all of the following criteria:

1. *Microscopically confirmed diagnosis of bronchogenic carcinoma.*—Microscopic diagnosis is based on an adequate biopsy sample or on sputum cytology, permitting classification by cell type. Classification by cell type follows the recommendations of the World Health Organization as advanced by Kreyberg (15) and amended at the International Workshop (table 2). The extent of differentiation should be stated for epidermoid carcinoma and adenocarcinoma. Most of the other subclassifications for small cell carcinoma, adenocarcinoma, and large cell carcinoma might remain optional until their prognostic implications are elucidated. Some patients, especially those with adenocarcinoma, including the bronchioloalveolar type, will require extensive diagnostic work-up to exclude extrapulmonary primary tumors. Pathology review panels are useful for decrease of observer variability (16,18). It is not recommended to admit patients with cytologic proof of bronchogenic carcinoma *without* cytologic or bioptic definition of the cell type.
2. *Stage of disease.*—The patient must be surgically (or medically) inoperable. Early stages might be more responsive than late ones. Thus, 12 of 17 (71%) patients with lymph node metastases responded to CCNU [4] as opposed to six of 32 (19%) patients with distant hematogenous metastases (21).
3. *Measurable or evaluable disease.*—Measurable or evaluable disease must be present and was found in 82% of 44 patients at the author's own service (19). Objective evaluation of evaluable but unmeasurable disease is described elsewhere (20).
4. *Objective evidence of progressive disease.*
5. *Prior therapy.*—Patients with prior exposure to the study drug or to the same class of drugs are excluded. The same holds true for patients with prior radiotherapy to all measurable or evaluable lesions. All reversible toxicity from prior radiotherapy

[4] CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

TABLE 2.—Microscopic classification of lung cancer

World Health Organization (15)	Suggested amendments, including code for data retrieval (16,17)
I. Epidermoid carcinoma	10. Epidermoid carcinoma
	11. Well-differentiated epidermoid carcinoma
	12. Moderately well-differentiated epidermoid carcinoma
	13. Poorly differentiated epidermoid carcinoma
II. Small cell anaplastic carcinoma	
1. Fusiform cell type	(see below, 22)
2. Polygonal cell type	(see below, 22)
3. Lymphocyte-like ("oat cell") type	21. "Oat cell" or lymphocyte-like
4. Others	22. Intermediate (polygonal/fusiform) cell type
III. Adenocarcinoma	30. Adenocarcinoma
1. Bronchogenic	31. Well-differentiated adenocarcinoma
a. Acinar *b.* Papillary	32. Moderately well-differentiated adenocarcinoma
2. Bronchioloalveolar	33. Poorly differentiated adenocarcinoma
	34. Bronchioloalveolar
IV. Large cell carcinoma	40. Large cell carcinoma
1. Solid tumors with mucin-like content	
2. Solid tumors without mucin-like content	
3. Giant cell carcinomas	41. Giant cell carcinomas
4. "Clear" cell carcinomas	42. "Clear" cell carcinomas
V.–XIII. Others	50. Others

and chemotherapy must have abated. Most cooperative study groups require a time interval of at least 2 weeks between treatments, although intervals of up to 2 months have been recommended (11). Exclusion of patients who had received prior treatment other than surgery is optional, based on suggestive evidence for higher response rates in previously untreated patients (5). Phase II studies with crossover design should help clarify this point.

6. *Performance status.*—Statements on performance status are optional. Most investigators require an estimated life expectancy of at least 2 months. Predictions are difficult. It is proposed to replace prognostication with performance status, in order to exclude totally bedridden (or bedridden and semiambulatory) patients (table 3) (11, 22).

7. *Adequate organ functions.*—Criteria depend on toxicity and route of excretion of the study compound. Leukocyte counts greater than or equal to 4000 or 5000 cells/mm^3 and thrombocyte counts greater than or equal to 100,000 platelets/mm^3 are required for myelosuppressive drugs. Serum creatinine levels of less than 1.6 mg/100 ml for drugs with renal excretion and bilirubin levels of less than 2 mg/100 ml for drugs with biliary excretion are usually required.

8. *Other primary malignant tumors.*—Concurrent presence of a second malignant tumor excludes the patient because results are usually not evaluable.

TABLE 3.—Evaluation of performance status

Karnofsky scale (7)		Zubrod scale (5)	
Description	Scale (%)	Grade	Description
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities; minor signs or symptoms of disease	90	1	Symptoms but nearly fully ambulatory
Normal activity with effort	80		
Cares for self; unable to carry on normal activity or to do active work	70	2	Some bed time, but needs to be in bed less than 50% of normal daytime
Requires occasional assistance but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed more than 50% of normal daytime
Disabled; requires special care and assistance	40		
Severely disabled; hospitalization indicated though death not imminent	30	4	Unable to get out of bed
Very sick; hospitalization necessary; active supportive treatment necessary	20		
Moribund	10		
Dead	0		

9. *Pregnancy.*—Pregnancy excludes the patient from the study because of possible untoward effects of treatment on the fetus.
10. *Informed consent.*—Written informed consent is required in the United States.

STUDY PARAMETERS

1. General

History and physical examination, including weight, height, body surface area, complete blood cell count, and thrombocyte count, should be recorded. Differential count is optional. The following tests should be performed: serum creatinine, urinalysis, uric acid, blood urea nitrogen, optimal bilirubin, serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, albumin/total protein, Na, K, Cl, Ca, and P. Other tests should be performed as clinically indicated.

2. Tumor

Staging is imperative for prognosis, therapy, and quantitation of response. Minimum requirements include chest film, posteroanterior and lateral; isotopic bone scan; bone films of areas with positive scan; and bone marrow needle biopsy (Vim-Silverman) and aspirate (posterior iliac crest or area of positive scan), imperative for all except epidermoid carcinoma. Optional procedures include bronchoscopy for estimation of endobronchial involvement; mediastinoscopy; brain scan, EEG, angiogram; and liver scan (metastases of the liver must be proven by needle biopsy). Other procedures as indicated.

The use of tumor-produced marker substances is under investigation. Information on the expected yield of the above named tests is described elsewhere (23).

The size and extent of the primary tumor and of metastases is mapped, and the number of metastatic lesions is counted per site. Up to five representative lesions are selected for measurement by calipers, using the longest and the widest perpendicular diameter. The data can be summarized on a Staging Form such as the form developed by D. Carr, based on the recommendations of the American Joint Committee on Staging (24) and extended to satisfy the needs of the radiotherapist and chemotherapist.

3. Host

Performance.—Performance has important prognostic implications. Two performance

scales are in common use: the percent scale by Karnofsky (7), where 100% equals normal performance and 0% equals death; and a numerical scale, where 0 equals normal and 4 denotes a patient who is completely bedridden (5). The latter scale is in wide use by cooperative study groups. A suggested key for intercomparison of both scales is given in table 3.

Weight change.—A notation of "normal weight," prior to the present disease and a notation of present weight should be made. Notation of edema, where present, is recommended.

Immunologic status.—A battery of skin tests is recommended. Commonly used tests include tuberculin (PPD, intermediate strength, containing 0.0001 mg/0.1 ml of solution); candidin, in a 1:100 dilution of full strength antigen; mumps antigen; and streptokinase-streptodornase. The possible impact of the immunologic status is exemplified in a recent study with CCNU (21), where 12 of 17 patients with positive ($\geq$1 cm) skin reaction responded, as opposed to one of 18 patients in the nonreactive group. The difference was statistically significant ($P<0.05$).

Serial observations.—These observations are obtained at appropriate intervals. Suggested minimum requirements for serial observations are listed in table 4 and should be amended for drugs with unusual toxicity. Serial observations are entered on flow sheets (used by members of the Working Party for Therapy of Lung Cancer and the Eastern Cooperative Oncology Group).

Drug administration.—The study drug is given at a predetermined dose schedule. The schedule depends on considerations such as mode of action, optimal schedule in experimental tumors, and toxicologic data of the phase I trial. The starting dose corresponds to the moderate reversible toxic dose of the phase I trial. Subsequently, the drug dose is adjusted to individual tolerance, such as leukopenia of 3000–4000 cells/mm^3. The drug dose is usually given in milligrams per square meter

TABLE 4.—Serial observations (suggested minimum requirements)

Parameter	Immediate pretreatment and post-treatment	Weekly	q2wks	q4–6wks
Tumor measurement				
Palpable lesion(s)	x	x		
Enumeration of lesions	x		x	
Chest film: posteroanterior and lateral	x		x*	
Bone marrow	x			x*
Bone scan	x			x*
Bone films	x*			x*
Brain scan	x*			x*
Host reaction				
Performance	x	x		
Body weight	x	x		
Immunologic status	x			x
Laboratory tests				
Hematocrit or hemoglobin	x		x	
Wbc, platelets	x	x†		
Creatinine	x	x		
Bilirubin, SGOT, alkaline phosphatase	x	x		
Albumin/total protein	x			x
Na, K, Cl, Ca, P	x			x
Urinalysis	x		x	

*In the presence of measurable or evaluable lesions.
†More frequent with daily or semiweekly drug administration.

body surface area. Surface area is preferred over body weight because of better comparability in patients with extreme weight changes, in adults, and in children.

Drug treatment is administered according to the following conditions:

a. Downward modification of drug dose to two thirds (or one half) of the offending dose is indicated in the presence of leukopenia ($\geq$3,000 cells/mm^3) or thrombocytopenia (50,000–$\leq$ 100,000 platelets/mm^3). Full dose is resumed as toxicity clears.

b. Treatment is interrupted in the presence of leukopenia (<3000 cells/mm^3) or thrombocytopenia (<50,000 platelets/mm^3), oral ulcerations, or diarrhea, and is re-instituted at a reduced dose level (two thirds or one half of full dose) as toxicity clears. Full dose can be resumed after tolerance of the reduced dose level for 1 week (longer for drugs with delayed toxicity). A return to full dose is not recommended after severe toxicity.

c. Increase of drug dose is considered in the absence of toxicity (other than transient nausea or vomiting). In this case, drug dose is increased in increments of 33% every 3 weeks (slower for drugs with delayed toxicity).

d. The duration of treatment depends on the antitumor response. Drug treatment might be stopped after 4 weeks in the presence of pronounced toxicity *and* progressive disease. In patients with objective response or static disease, treatment should be continued until progressive disease occurs. Patients should be followed for at least 2 weeks after the last dose for observation of toxicity.

e. Treatment can be stopped at any time by a senior investigator, if this is clearly in the best interest of the patient. Circumstances need thorough documentation.

SUPPORTIVE THERAPY

1. *General.*—Vigorous supportive therapy of intercurrent complications is recommended as long as patients have a reasonable chance of meaningful clinical benefit from treatment.
2. Radiotherapy is permissible for vital indications or for relief of otherwise uncontrollable, tumor-related, severe pain. Radiotherapy to the only measurable or evaluable lesion results in disqualification of the patient from the phase II study.
3. Chemotherapy with other than the study drug(s) disqualifies the patient. This includes the use of mithramycin or actinomycin D[5] for treatment of hypercalcemia.
4. Corticosteroids can be used for short time intervals for vital indications such as the control of cerebral edema. Prolonged, elective use of corticosteroids shortens survival when compared to placebo-treated controls (25) and therefore leads to disqualification.
5. Cerebral metastases are best treated with radiotherapy to the entire brain. Current practice at the author's service includes treatment up to a dose of 5000 R over 5 weeks (R. Andrews). Treatment to smaller ports or at lower equivalent doses proved less satisfactory.

MEASUREMENT OF RESPONSE

Quantitation of response relates to the tumor, to tumor-related host functions, and to symptomatology. The measurement is obtained by calipers, using the product of the longest tumor diameter times the widest perpendicular diameter. Evaluable, nonmeasurable lesions require marked, almost complete regression to qualify for response. Chest films with evaluable lesions are blinded as to date and patient identification and are presented in series of three or more films to an expert committee. Objective response is denoted when there is unanimous agreement on the chest film with the smallest lesion and when this film is obtained after the start of therapy.

[5] Mithramycin: NSC-24559; CAS reg. No. 18378-89-7. Actinomycin D: NSC-3053.

Objective tumor response.—Objective tumor response is graded as follows:

1. Complete regression denotes disappearance of all recognizable tumor lesions.
2. Partial regression includes $\geq 50\%$ regression of one or more measurable lesions or marked ($\geq 75\%$) regression of evaluable, nonmeasurable lesions in the absence of progression elsewhere or occurrence of new lesions. (Some investigators and cooperative study groups define partial regression as $\geq 50\%$ regression of *all* measured lesions in the absence of new lesions. Such a definition appears suboptimal for purposes of a phase II protocol in lung cancer because of the known significant difference of response by organ site, as established for gastrointestinal cancer [26] and because of the difficulty in quantifying response of bone marrow lesions.) The use of a category for "improvement," denoting 25%–49% tumor regression, is not recommended, because it is difficult to recognize such minor changes on chest films (20). Instead, it is desirable to include such patients in the category "static tumor."
3. *Static tumor* includes changes of less than $\pm 50\%$ ($<75\%$ decrease or 100% increase for evaluable, nonmeasurable lesions) in the absence of new lesions. Arrest of tumor growth implies a cell kill equivalent to new growth and was shown to relate to survival gain in patients with bronchogenic carcinoma (27,28) and breast cancer (29).
4. *Tumor progression* is documented by any of the following changes: occurrence of any new lesion, irrespective of response elsewhere; increase of $\geq 50\%$ of a measurable lesion; or increase of $\geq 100\%$ of an evaluable lesion. Cerebral metastases are the exception to the rule: occurrence or progression of cerebral metastases without tumor progression elsewhere is not interpreted as treatment failure because of an assumed blood-brain barrier for most of the commonly used antineoplastic agents.

Tumor-related host functions.—Abnormal, potentially tumor-related host functions such as hypercalcemia, increased SGOT, or anemia should return to normal when complete tumor regression advances to a complete remission. Without objective response, these host functions are not taken as evidence of response or progression of disease. Body weight is the exception to this rule: weight loss of $\geq 10\%$ over 1 month, unrelated to disappearance of edema or dehydration, is accepted as evidence for progressive disease, even if measurable or evaluable lesions are static.

Symptomatic improvement.—Improvement of $\geq$ one grade or $\geq 20\%$ (table 3) is regarded as meaningful but does not denote objective response. Complete disappearance of tumor-related symptoms is necessary for "complete remission" over and above complete tumor regression.

TIME FACTORS

1. Duration of treatment: time from the first drug dose to the last drug dose, irrespective of interruptions of treatment.
2. Duration of study: time from the first drug dose to the last drug dose plus 14 days or until toxicity clears, whichever is longer.
3. Duration of response: from the first day of objective response until the day before progression of disease is noted.
4. Time to progressive disease: from the first day of treatment to the day before progression is noted.
5. Survival: from the first day of treatment until death.

CRITERIA FOR INVALIDATION

1. Ineligibility: any patient who does not meet one or more criteria for patient selection.
2. Major violation of the protocol: major deviations from the protocol such as changes of drug dose or dose schedule, or use of other antineoplastic drugs; in randomized studies, violation of randomization procedures.

3. Submission of inadequate records: the chairman might wish to disqualify a patient if three requests for submission of records or of pertinent data remain unanswered. Later submission of records might requalify.
4. Loss to followup is reason for disqualification, if it occurs unrelated to treatment before response can be reasonably expected. Early death or refusal of the patient to continue treatment are regarded as treatment failures.

RECORDS TO BE KEPT

1. On-study information
2. Flow sheet
3. Tumor measurement sheet (optional), if information on flow sheet is regarded as insufficient
4. Summary form
5. Pathology form
6. Autopsy form

(Samples of these forms can be obtained through Mrs. Bernice Brown, Office Manager, Working Party for Therapy of Lung Cancer, 850 Sligo Ave., Suite 600, Silver Spring, Md 20910.)

Background.—Short summary of pertinent data on study drug should include chemical data, stability, solubility, and storage requirements; schedule dependency; mode of action; pharmacology and toxicology; antidotes, where available; therapeutic benefit against human tumors.

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APPENDIX 1

Protocol Number
Group or Institution(s)
Activated (date)
Revised (date)
Priority among other current studies (No.) _____
Closed to entry of new patients (date)

PHASE II: INITIAL THERAPEUTIC TRIAL OF NEW DRUGS IN LUNG CANCER

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11. Background
12. References

Study Plan: Give scheme of plan, including drug, dose, route, schedule, and duration.
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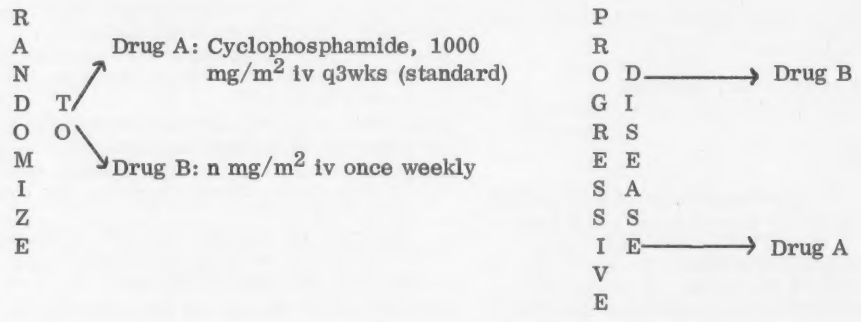

Study Chairman (name, address, telephone number)
Drug Procurement Through (source)

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New Agents and Combinations in the Treatment of Bronchogenic Carcinoma

Gerald P. Bodey, Jeffrey A. Gottlieb, Robert Livingston, and Emil Frei III [1,2]

SUMMARY

Phase I and II studies have been conducted with various combinations of vincristine, bleomycin, methyl-CCNU, and cyclophosphamide in the treatment of bronchogenic carcinoma. Although bleomycin alone was not very active, the combination of vincristine and bleomycin produced three partial responses in 12 patients. Methyl-CCNU alone produced four partial responses in 16 patients, whereas the combination of methyl-CCNU and cyclophosphamide produced three partial responses in ten patients. Preliminary studies have been initiated with the four drugs in combination and five of 13 patients have achieved partial responses. Major toxic effects have included nausea, vomiting, skin changes, neuropathy, and myelosuppression. Further studies with this combination are warranted.

[Cancer Chemother Rep Part 3, vol 4:227–229, 1973]

Progress in the chemotherapy of bronchogenic carcinoma has been slow. However, in recent years there have been a few accomplishments which offer hope for greater future success in the treatment of the disease. Among the important contributions have been the development of an experimental animal tumor model, the Lewis lung carcinoma; the recognition of the prognostic importance of cell type in bronchogenic carcinoma; the introduction of combination chemotherapy; the discovery of new antitumor agents; and the introduction of immunotherapy.

Phase I and II chemotherapeutic studies have been initiated at our institution utilizing several new agents alone and in combination. Prompted by initial reports in the Japanese literature of moderate success with bleomycin (NSC-125066) in patients with extensive bronchogenic carcinoma, a phase II study of this drug was undertaken by members of the Southwest Cancer Chemotherapy Study Group (1). Bleomycin was administered semiweekly either intravenously (iv) or intramuscularly (im) at a dose level of 10 mg/m² of body surface area to 68 patients with bronchogenic carcinoma (table 1). Forty-four patients received what was considered to be an adequate trial, which was 3 weeks of treatment. There were only three responses: one complete remission in a patient with adenocarcinoma and two partial responses (one patient with epidermoid carcinoma and the other with adenocarcinoma). Patients were considered to have had a partial response if there was a greater than 50% reduction in the two widest diameters of the tumor masses during chemotherapy.

Recent studies have demonstrated that synchronized hamster ovarian cells in tissue culture are most sensitive to the effects of bleomycin

[1] Department of Developmental Therapeutics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

[2] Dr. Bodey is a Scholar of the Leukemia Society of America, Inc.

TABLE 1.—Bleomycin alone in the treatment of bronchogenic carcinoma

No. of patients—	Bronchogenic carcinoma cell type			
	Epidermoid	Adeno-carcinoma	Oat cell	Total
Entered	35	9	24	68
With adequate trial	22	8	14	44
With complete remissions	0	1	0	1
With partial responses	1	1	0	2

TABLE 2.—New agents and combinations in the treatment of bronchogenic carcinoma

Treatment	No. of patients—		
	Entered	With adequate trial	With partial response
Bleomycin alone	68		3*
Bleomycin + vincristine	12	12	3
Methyl-CCNU alone	16	13	4
Methyl-CCNU + cyclophosphamide	10	10	3
COMB †	13	12	5

* One complete remission.

† COMB = cyclophosphamide, vincristine (Oncovin), methyl-CCNU, and bleomycin.

during mitosis.[3] Vincristine [4] causes an accumulation of cells in mitosis, probably through damage to a mitotic spindle precursor in late S or G_2 phase of the cell cycle (2). This effect of vincristine reaches a maximum at 6–12 hours after administration in human bone marrow and solid tumors (3). Consequently, a study of the combination of vincristine and bleomycin was started at our institution (4). Vincristine was administered iv at a dose level of 1 mg (0.75 mg for patients over 50 years old), followed 6 hours later by 20 mg/m² of bleomycin given im (maximum dose 35 mg). This regimen was given semiweekly for 6 weeks, after which time the patients were evaluated for antitumor response and were given other therapy. This change in therapy was necessitated by the potentially fatal pulmonary toxic effects of bleomycin at total doses exceeding 300 mg. Twelve patients with bronchogenic carcinoma were entered into this preliminary study (table 2). Three achieved partial responses and an additional seven demonstrated some objective improvement which was less than a partial response. Major toxic effects from this regimen included nausea, vomiting, skin changes, alopecia, and neuropathy. No unexpected toxic effects occurred as a result of the use of these two drugs in combination. Although this was only a small study, the results were much more encouraging than those obtained with bleomycin alone and suggested that this combination of bleomycin and vincristine might be incorporated into other regimens in the treatment of bronchogenic carcinoma.

While the above study was in progress, another promising lead was being investigated. Mayo et al (5) had shown that methyl-CCNU,[5] a new oral nitrosourea, was considerably more effective in the treatment of advanced Lewis lung carcinoma in the rodent than other nitro-

[3] Frei E III, Saunders P, and Barranco S. Unpublished observations.

[4] Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1); Oncovin.

TABLE 3.—COMB* in the treatment of bronchogenic carcinoma

No. of patients—	Bronchogenic carcinoma cell type			
	Epidermoid	Adeno-carcinoma	Oat cell	Total
Entered	5	6	2	13
With adequate trial	5	6	1	12
With partial responses	2	2	1	5

*COMB = cyclophosphamide, vincristine (Oncovin), methyl-CCNU, and bleomycin.

soureas or conventional chemotherapeutic agents. Methyl-CCNU was administered orally at a dose level of 200 mg/m² every 6 weeks to 16 patients with bronchogenic carcinoma (table 2). Four of the 13 patients who received an adequate trial (two or more courses) achieved a partial response (one of four with epidermoid carcinoma and three of eight with adenocarcinoma). One patient with oat cell carcinoma did not respond. Major toxic effects included nausea, vomiting, and myelosuppression.

Subsequently, Mayo et al (5) also demonstrated that the combination of methyl-CCNU and cyclophosphamide [6] was highly synergistic against Lewis lung carcinoma. A phase I study of this combination at our institution included ten patients with bronchogenic carcinoma. Methyl-CCNU was administered orally at a dose level of 100 mg/m² and cyclophosphamide was administered iv at a dose level of 1 g/m². Both drugs were repeated at 6-week intervals. Three of the ten patients achieved partial responses (table 2). Toxic effects were mainly nausea, vomiting, and myelosuppression.

Since both the combination of vincristine and bleomycin and the combination of methyl-CCNU and cyclophosphamide appeared promising in the treatment of bronchogenic carcinoma, a four-drug regimen was developed. This combination, COMB,[7] is especially appealing since the drugs have independent toxic effects and can be administered together at optimal dose levels. Vincristine was given iv at a dose level of 1 mg followed 6 hours later by 30 mg of bleomycin given iv, 100 mg/m² of methyl-CCNU given orally, and 1 g/m² of cyclophosphamide given iv. Vincristine and bleomycin were continued semiweekly for 6 weeks and methyl-CCNU and cyclophosphamide were administered at 6-week intervals. At the present time 31 patients with bronchogenic carcinoma have been entered into this study and 12 are evaluable. Five patients have achieved partial responses (tables 2 and 3). Major toxic effects have been nausea, vomiting, skin changes, neuropathy, and myelosuppression. No unexpected toxic effects have occurred from the use of this combination.

These preliminary studies suggest promising avenues of investigation. An extensive comparative study of the four-drug regimen with methyl-CCNU plus cyclophosphamide and with methyl-CCNU alone should be undertaken to ascertain which of these regimens is the most effective in bronchogenic carcinoma.

[5] Methyl-CCNU: NSC-95441; CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-.

[6] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

[7] COMB: cyclophosphamide, vincristine (Oncovin), methyl-CCNU, and bleomycin.

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Chemotherapy of Lung Cancer: The Experience of the National Cancer Institute of Milan

Gianni Bonadonna, Gabriele Tancini, and Emilio Bajetta[1,2]

During the past decade at the National Cancer Institute of Milan, chemotherapy of advanced bronchogenic carcinoma has included treatment with single agents given sequentially and, more recently, with multiple drugs given in combination. No major programs have been developed involving the simultaneous or sequential use of chemotherapy plus radiotherapy administered in a prospective controlled clinical trial. The use of radiotherapy in patients receiving chemotherapy was usually limited to the occurrence of superior vena cava compression syndrome or to bone pain secondary to metastatic deposits.

The primary aim of the present report is to summarize the results obtained from 1967 to 1970 with some of the new drugs tested in lung cancer. The preliminary results of a multiple-drug treatment program started in 1971 will also be included. Our experience with alkylating agents does not seem to be substantially different from that already published in the literature (1). For this reason, the results obtained with mechlorethamine and cyclophosphamide are omitted from the present report.[3]

Median survival time is still the most significant measure of the effect of a given therapy. However, in the present report the survival time has not been calculated since nearly all patients received other chemotherapeutic agents before and/or after the experimental drug was given.

SINGLE-AGENT CHEMOTHERAPY

During phase I and II studies from 1967 to 1970, three new drugs (hydroxyurea, adriamycin, and bleomycin) have been tested in the treatment of advanced lung cancer. During the same period of time two studies with methotrexate and procarbazine given intravenously were also undertaken. Most of the patients selected for these types of studies had already received prior therapy with one or two conventional agents. Although the disease had shown definite signs of progression, often with symptoms and distant metastases, in no instance was the performance status below 40 (2).

Complete tumor remission was defined as the complete disappearance of all recognizable tumor masses for at least 1 month. Partial remission included two categories: greater than or less than 50% decrease of one or more tumor lesions for at least 1 month in the absence of progression or occurrence of new lesions elsewhere. Although changes of less than 50% are usually discounted (error of different projections or penetration, bias of measurement), they have been considered in this report in the overall response rate.

Static disease was defined as no change in tumor volume. No response was defined as progressive disease with the occurrence of a new lesion or the increase in any measurable lesion by at least 25%, regardless of regressions elsewhere.

In both responsive and nonresponsive patients treatment was continued until unequivocal signs of progression occurred.

Hydroxyurea

Table 1 summarizes the results obtained with different doses of hydroxyurea given iv (3). The overall response rate was 29% but in only two patients (7%) was a consistent regression observed (partial regression >50% in one patient and complete regression in another). The most effective schedule was 100 mg/kg given on alternate days. Although the drug was usually

[1] National Cancer Institute of Milan, Italy.

[2] *Reprint requests to:* Dr. Gianni Bonadonna, Via Venezian 1, Milan 20133, Italy.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

TABLE 1.—Results of phase I study with hydroxyurea

Dose schedule (iv)	No. of evaluable patients	Response				Mean duration (mos)
		None	25%–50%	>50%	Complete	
10 mg/kg/day	3	3				
40 mg/kg/day	15	11	3	1		2.5
100 mg/kg/day	3	3				
100 mg/kg on alternate days	6	2	3		1	6.2
Total	27	19	6	1	1	

tolerated fairly well, bone marrow toxicity represented the dose-limiting factor.

Adriamycin

This new antitumor antibiotic, structurally related to daunorubicin, underwent an extensive clinical trial at the National Cancer Institute of Milan (4,5). A preliminary clinical screening (6) showed that adriamycin was more effective than daunorubicin (7) in the treatment of lung cancer. When more data on bone marrow toxicity became available (in a subsequent study carried out in cooperation with the Southwest Cancer Chemotherapy Cooperative Study Group) the drug was given at a dose of 25 mg/m² for 3 consecutive days and the courses were repeated every 3 weeks.

Table 2 reports the therapeutic results obtained with adriamycin in bronchogenic carcinoma. The overall response rate was 48% and the consistent regression rate was 9%. The most effective therapeutic schedule appeared to be that in which the drug was given at 3-week intervals. Regressions were observed in all cell

TABLE 2.—Results of phase I–II study with adriamycin

Dose schedule (iv)	No. of evaluable patients	Response				Mean duration (mos)
		None	25%–50%	>50%	Complete	
0.4 mg/kg × 3/wk	10	7	3			1.5
0.6 mg/kg × 3/wk	9	3	4	2		2.0
25 mg/m² × 3 q3wks	18	9	7	1	1	3.0
Total	37	19	14	3	1	

TABLE 3.—Response to adriamycin in relation to cell type

Cell type	No. of patients	Response			
		None	25%–50%	>50%	Complete
Epidermoid carcinoma	9	2	7		
Adenocarcinoma	6	4	2		
Undifferentiated carcinoma (small cell)	5	3		2	
Undifferentiated carcinoma (large cell)	11	7	2	1	1
Unclassified	6	3	3		
Total	37	19	14	3	1

TABLE 4.—Results of phase I–II study with bleomycin

Dose schedule (iv)	No. of evaluable patients	Response		Mean duration (mos)
		None	25%–50%	
15 mg/m²/day × 5	4	3	1	1
15 mg/m²/day × 8	4	2	2	1.4
30 mg/m²/day × 8	4	3	1	1
30 mg/m² × 2/wk	3	3		
Total	15	11	4	

types (table 3), but consistent responses occurred only in undifferentiated carcinomas. The dose-limiting factor was severe myelosuppression. Symptomatic cardiac toxicity represents a potential harmful side effect especially if the total dose is greater than 600 mg/m² (5). Irreversible acute cardiac failure was observed in one patient with lung cancer during treatment with adriamycin (total dose, 470 mg/m²).

Bleomycin

Japanese clinical studies (8) have found bleomycin to be effective in all types of epidermoid carcinoma including those originating from the bronchi. For this reason, our phase I–II evaluation of this drug included 15 patients with lung cancer (9). Table 4 reports the therapeutic results after four different dose schedules. Only a marginal regression rate for a very limited period of time was observed. The four responsive patients had either epidermoid carcinoma or undifferentiated small cell carcinoma (table 5). The dose-limiting factor with the use of bleomycin was delayed pulmonary toxicity (9,10).

Methotrexate

Table 6 reports the results in lung cancer of large intermittent iv doses of methotrexate (11). The overall regression rate was 58%; however, in only two patients was a consistent regression observed, and the mean duration of response for all patients was less than 2 months. The response related to cell type (table 7) showed that the regression rate was 61% for epidermoid carcinoma, 66% for adenocarcinoma, and 100% for undifferentiated small cell carcinoma. No regressions were observed in undifferentiated large cell carcinoma. No comparison could be made between the two dose schedules employed. In fact, only six patients received 60 mg/m² because of severe gastrointestinal, bone marrow, and renal toxicity (11).

Procarbazine

The results obtained with procarbazine administered as a single agent in advanced lung cancer are reported in table 8. At the daily iv dose level of 4 mg/kg the overall response rate was 34%. No complete remissions were seen. Responses were observed in epidermoid and undifferentiated small cell carcinoma (table 9). At this dosage a mild degree of leukopenia was observed in only two of 26 patients, while nausea and vomiting represented the major toxic effect, especially during the first week of drug administration.

COMBINATION CHEMOTHERAPY

Two trials with combination chemotherapy in lung cancer have been carried out at the

TABLE 5.—Response to bleomycin in relation to cell type

Cell type	No. of patients	Response	
		None	25%–50%
Epidermoid carcinoma	10	8	2
Adenocarcinoma	2	2	
Undifferentiated carcinoma (small cell)	3	1	2
Total	15	11	4

TABLE 6.—Results of phase II study with intermittent methotrexate

Dose schedule (iv)	No. of evaluable patients	Response				Mean duration (mos)
		None	25%–50%	>50%	Complete	
40 mg/m²/wk	30	12	16	1	1	1.6
60 mg/m²/wk	6	3	3			1.5
Total	36	15	19	1	1	

TABLE 7.—Response to intermittent methotrexate in relation to cell type

Cell type	No. of patients	Responsive patients		
		40 mg/m²	60 mg/m²	Total
Epidermoid carcinoma	18	11/17	0/1	11
Adenocarcinoma	6	2/3	2/3	4
Undifferentiated carcinoma (small cell)	3	2/2	1/1	3
Undifferentiated carcinoma (large cell)	4	0/3	0/1	0
Unclassified	5	3/5		3
Total	36	18/30	3/6	21

TABLE 8.—Results of phase II study with procarbazine plus 5-fluorouracil

Drug	Dose schedule (iv)	No. of evaluable patients	Response				Mean duration (mos)
			None	25%–50%	>50%	Complete	
Procarbazine	4 mg/kg/day	26	17	7	2		2.5
Procarbazine + 5-FU	4 mg/kg/day + 10 mg/kg on alternate days (iv push)	24	9	9	4	2	2.5
Procarbazine + 5-FU	4 mg/kg/day + 10 mg/kg on alternate days (2-hr infusion)	12	8	3	1		3.5
Total		62	34	19	7	2	

TABLE 9.—Response to procarbazine plus 5-fluorouracil in relation to cell type

Cell type	No. of patients	Responsive patients	
		Procarbazine alone	Procarbazine + 5-FU
Epidermoid carcinoma	19	3/8	6/11
Adenocarcinoma	11	0/5	5/6
Undifferentiated carcinoma (small cell)	11	1/2	4/9
Unclassified	21	5/11	4/10
Total	62	9/26	19/36

National Cancer Institute of Milan. The first study included procarbazine plus 5-fluorouracil (5-FU); the second included a multiple-drug combination with most of the agents found to be effective in lung cancer.

Table 8 summarizes the results of the first trial. Patients were randomly assigned to receive (*a*) procarbazine alone, (*b*) procarbazine plus 5-FU given on alternate days by rapid iv injection, or (*c*) procarbazine plus 5-FU administered on alternate days via a 2-hour iv infusion. The combination of procarbazine and 5-FU given rapidly iv proved to be the most effective treatment (overall regression rate, 62%) while the same combination with 5-FU given slowly iv yielded an overall regression rate (33%) similar to that obtained with procarbazine alone (34%). The only advantage of giving 5-FU via a 2-hour infusion was represented by the absence of leukopenia in all patients during the entire course of treatment. The response related to cell type showed regressions in all cell types, but particularly in adenocarcinoma (table 9).

Figure 1 outlines the schema of the combination chemotherapy protocol for advanced bronchogenic carcinoma presently in use at the National Cancer Institute of Milan. The drugs and their dosages were selected on the basis of results obtained during phase II studies, as summarized previously. In regimen A two triple combinations were alternated with an interval of 2 weeks between each treatment course. In the triple combination with mechlorethamine, methotrexate, and adriamycin, all drugs were administered iv on Day 1. In the second triple combination, 5-FU and hydroxyurea were given orally on alternate days (the latter in divided doses every 8 hours), while procarbazine was administered daily orally for 2 weeks. When progression occurred patients receiving regimen B received treatment with 5-FU, hydroxyurea, and procarbazine.

The preliminary results in relation to cell type are reported for both regimens in tables 10 and 11. Due to the limited number of patients enrolled so far in the study, no conclusions can be drawn. However, with regimen A no complete remissions have been observed in the 13 patients entered in the study, while with regimen B two of 13 patients have achieved complete remission. Furthermore, the mean duration of response has been higher in regimen B than in regimen A.

COMMENTS

In general, chemotherapy of nonresectable lung carcinoma, despite numerous adequate studies, has been poorly rewarding in terms of percent of complete remission and prolongation of survival. A review of our patients who were also treated with some of the new drugs, such

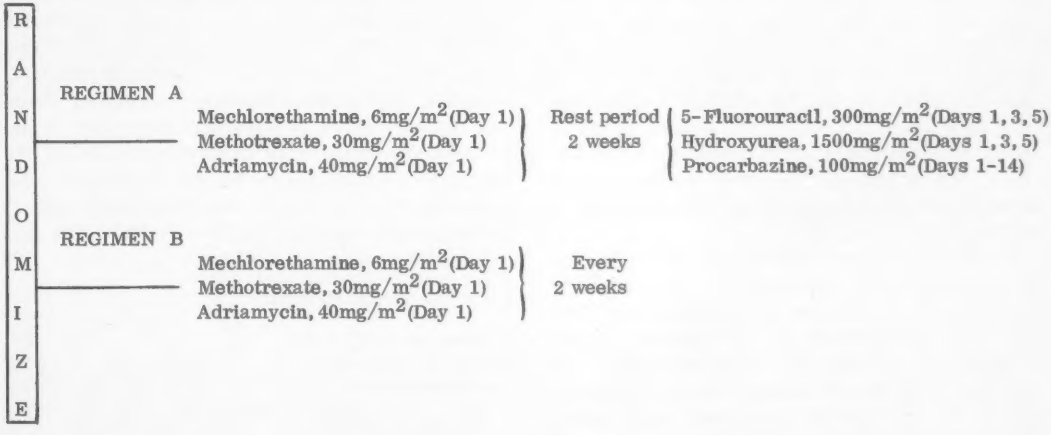

FIGURE 1.—Combination chemotherapy in lung cancer.

TABLE 10.—Combination chemotherapy: preliminary results of regimen A in relation to cell type

Cell type	No. of patients	Response			Mean duration (mos)
		None	25%–50%	>50%	
Epidermoid carcinoma	5	4	1		1
Adenocarcinoma	2	2			
Undifferentiated carcinoma (large cell)	3	1		2	2.5
Unclassified	3		2	1	2+
Total	13	7	3	3	

TABLE 11.—Combination chemotherapy: preliminary results of regimen B in relation to cell type

Cell type	No. of patients	Response				Mean duration (mos)
		None	25%–50%	>50%	Complete	
Epidermoid carcinoma	2	1			1	5+
Adenocarcinoma	4	1	3			5+
Undifferentiated carcinoma (small cell)	2	1		1		2
Undifferentiated carcinoma (large cell)	1				1	8+
Unclassified	4	4				
Total	13	7	3	1	2	

as adriamycin and bleomycin, confirms the general impression that advanced bronchogenic carcinoma can seldom be controlled with single-agent chemotherapy. Although a number of encouraging results could be obtained in selected patients receiving high doses of drugs, such as methotrexate (13), and the effect of some drugs, such as adriamycin and the nitrosoureas, could be better defined through appropriate controlled trials, the experience achieved so far clearly demonstrates that single-drug chemotherapy is only marginally effective.

A more sustained therapeutic response can be expected with combination chemotherapy and with the association of multiple-drug therapy with radiotherapy. In our opinion, proper selection of patients for controlled trials (in relation to extent of disease and performance status) is essential to prove that combination chemotherapy is clearly superior to single-agent chemotherapy in improving the percent of complete response and the duration of median survival.

It is also our opinion that prolonged combination chemotherapy plus radiation therapy should be more extensively tried in an earlier phase of the disease, ie, in surgically treated patients. Since bronchogenic carcinoma does not appear to be particularly amenable to a prolonged control with the available forms of therapy, the therapeutic efforts (including immunotherapy) should be concentrated in those patients with expected minimal residual disease after major surgical treatment.

LIST OF COMPOUNDS

Adriamycin: NSC-123127
Bleomycin: NSC-125066
Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate
Daunorubicin: NSC-83142; CAS reg. No. 23541-50-6; daunomycin (NSC-82151)

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8
Hydroxyurea: NSC-32065; CAS reg. No. 127-07-1
Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard
Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-
Procarbazine: NSC-77213; CAS reg. No. 491-88-3; *p*-toluamide, *N*-isopropyl-*α*-(2-methylhydrazino)-, monohydrochloride

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Should Initial Treatment of Small Cell Carcinoma Include Systemic Chemotherapy and Brain Irradiation?

Heine H. Hansen [1]

SUMMARY

The local treatment of small cell carcinoma of the lung is notoriously unsatisfactory. Treatment of all patients from the time of diagnosis with systemic chemotherapy and prophylactic irradiation of the brain is proposed. The rationale behind this approach is based on recent favorable experience with chemotherapy and on the increasing frequency of brain metastases with prolongation of survival.
[Cancer Chemother Rep Part 3, vol 4:239–241, 1973]

In general, the results of local therapy for small cell carcinoma of the lung have been disappointing compared with results obtained with other types of bronchogenic carcinoma. This is evident in the study conducted by the British Medical Research Council, in which patients with small cell carcinoma which was considered to be resectable were treated with either local radiotherapy or surgery. The mean duration of survival after treatment was 284 and 199 days, respectively, and the 5-year survival rate was 4% and 1%, respectively (1).

Increased experience with chemotherapy in the treatment of small cell carcinoma has resulted in the recognition of the responsiveness of this tumor to a number of chemotherapeutic agents (2). Prolongation of survival has been reported with cyclophosphamide [2] treatment alone in a controlled study (3). Our clinical studies using combinations of chemotherapeutic agents alone or with radiotherapy yielded a substantial improvement in median survival time (4). Other investigators have had a similar positive experience with either cyclophosphamide plus radiotherapy (5) or combination chemotherapy (6) in patients with small cell carcinoma. However, the occurrence of brain metastases contributes significantly to the failure rate of present therapy. Our experience with this problem is outlined in detail in the following section.

MATERIALS, METHODS, AND RESULTS

From May 1969 to December 1971, 22 untreated patients with unresectable small cell carcinoma were referred to the NCI–VA Medical Oncology Service for treatment. They underwent baseline staging procedures including bone marrow examination, skeletal X-rays and bone scans to define skeletal involvement, and brain scan.

The diseases of seven of the 22 patients were staged initially as limited to one hemithorax, which could include the pleura and extension to ipsilateral scalene nodes; the diseases of the remaining 15 patients were classified as extensive. Four of the patients in the latter group were found to have histologically documented hepatic metastases and ten were found to have bone marrow invasion; one of these patients and one other had evidence of brain involvement at the time of diagnosis. Initially, a combination of cyclophosphamide and methotrexate was used (4).[3] More recently,

[1] Bispebjerg Hospital, Copenhagen, Denmark.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

[3] Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl]-methylamino]benzoyl]-.

CCNU [4] has been added to the combination. In addition, radiotherapy (5000 rads in 5 weeks to the chest lesion) was given to patients with disease limited to the hemithorax. The overall median survival for all patients, irrespective of stage of disease, was 240 days (range, 51–949 days).

Brain metastases occurred in ten patients (45.5%) during the course of disease; neurologic manifestations became the major symptomatic feature in eight of these patients. The rate of appearance of the brain metastases is summarized in table 1. The risk of metastasis to the brain appears to increase progressively during the course of treatment.

DISCUSSION

In view of the clinical data presented, intensive systemic chemotherapy and prophylactic irradiation of the brain from the time of diagnosis appear to be indicated in the treatment of small cell carcinoma. The following postulates are the basis for this approach:

1. Small cell carcinoma is usually a systemic disease at the time the patient presents himself for treatment. Compared with other cell types of bronchogenic carcinoma, small cell carcinoma has a greater potential for early spread (invading mediastinal lymph nodes [7], bone marrow [8], and liver [9]) and has a higher proliferative fraction as demonstrated by cell kinetic studies (10).
2. Spread of the disease to the brain is common. Necropsy studies indicate the frequent spread of small cell carcinoma to the brain. In a recent series, the incidence of cerebral metastases was 42% and the metastases occurred most often as multiple metastases (11).
3. The chances of symptomatic brain metastases increase with prolongation of survival. This is suggested by the data presented and may be explained by the occurrence of dissemination prior to treatment. An analogy may be drawn to acute lymphoblastic leukemia where the brain may be acting as a "protective environment" for cancer cells otherwise susceptible to the chemotherapeutic agents. Intensive combination chemotherapy resulting in the prolongation of the median survival time led to the recognition of meningeal leukemia as a major therapeutic problem in patients otherwise achieving a systemic remission (12). Eventually, treatment directed to prevent this complication (prophylactic cerebrospinal irradiation and intrathecal administration of methotrexate) proved to be effective not only in preventing meningeal leukemia, but also in reducing systemic relapses and in prolonging the overall survival time (13,14).
4. Radiotherapy is effective in controlling cerebral disease. Experience with radiotherapy in patients with symptomatic brain metastases indicates favorable results in a high percentage of patients (15). Published reports on the use of radiotherapy in the treatment of brain metastases do not clearly distinguish between the different cell types of bronchogenic carcinoma. In the primary tumor, however, the small cell carcinoma is known to be relatively radiosensitive (16). Major neurologic deficits at the start of radiotherapy, however, adversely affect the outcome (17).
5. Increasingly effective chemotherapeutic schemes can be designed. Therapeutic ni-

[4] CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

TABLE 1.—Timing and risk of appearance of brain metastases

Time after diagnosis (mos)	No. of patients with brain metastases/ total No. of patients at risk	Percent
At the time of diagnosis	2/22	9.1
1–3	0/22	0
3–6	2/21	9.5
6–9	2/12	16.6
9–12	2/8	25.5
12	2/3	66.0
Total	10/22	45.5

hilism has to a great extent prevented extensive trials of chemotherapeutic agents at the earliest stages of disease. Identification of a constellation of drugs with reliable effectiveness raises hopes that an approach similar to that successfully used in Hodgkin's disease (18) may be found for small cell carcinoma. Combinations of effective chemotherapeutic agents need to be tested systematically. Serially determined tumor markers, including ectopic hormonal secretions and fetoplacental peptides, may provide the tools for the identification of successful tumor eradication.

In summary, application of a combination of local and systemic measures from the time of diagnosis would appear to offer the greatest possibility for a more sustained favorable outcome in patients afflicted with this prevalent malignant disease.

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Preliminary Clinical Assessment of ICRF 159 (NSC-129943) in Bronchogenic Carcinoma [1]

K. Hellmann [2]

ABSTRACT

ICRF 159 is a broad-spectrum antimitotic agent which also inhibits experimental metastases. It was therefore of particular interest to see whether it was useful in the treatment of carcinoma of the bronchus. In a preliminary clinical assessment, patients received either radiotherapy or radiotherapy plus ICRF 159. Of ten patients who received ICRF 159 plus radiotherapy but no maintenance chemotherapy, eight had excellent regressions (four with squamous cell, two with oat cell, and two with no histologic diagnosis). Of eight patients who had radiotherapy plus ICRF 159 with maintenance ICRF 159 afterwards, the mean survival time was 11.4 months (four still alive), compared with 8.3 months (two of six still alive) in patients who received radiotherapy only. Of those who received maintenance ICRF 159, only one had clinically detectable metastases.

[Cancer Chemother Rep Part 3, vol 4:243, 1973]

[1] ICRF 159: CAS reg. No. 21416-87-5; 2,6-piperazinedione, 4,4'-propylenedi-, (±)-.

[2] Department of Medicine, Imperial Cancer Research Fund, London, England.

Chemotherapeutic Drugs Marked With Radioactive Isotopes

Oliver Monod and Maurice Rymer [1]

SUMMARY

Therapeutic drugs can be marked with radioactive isotopes. Consequently, this method could be an aid to localize the fixation of these drugs, either in organs or tissues. Case reports are presented for six patients who received bleomycin marked with radioisotopes of cobalt 57, cobalt 55, copper 67, and mercury 197.

[Cancer Chemother Rep Part 3, vol 4:245–249, 1973]

The first experiments of this kind were carried out in many countries with cobalt 57 fixed on bleomycin (NSC–125066). The following are some preliminary clinical examples.

CASE REPORTS

Case No. 1.—Patient No. 1 was a 44-year-old man with secondary adenocarcinoma of the right upper lobe and primary cancer of the pancreas (fig 1). The test with bleomycin labeled with cobalt 57 was positive. The fixation ratio is the difference on the scintiscan between the intensity of fixation at the level of the lesion and fixation at the symmetric healthy level. From the diseased side to the other side, the fixation ratio was 2.8 at 4 hours after administration and 5 at 7 hours after administration (fig 2).

Case No. 2.—Patient No. 2 was a 60-year-old man with right upper lobe primary epidermoid cancer. The bleomycin-cobalt 57 test was positive (fig 3). The liver opacity was normal, since the liver and the kidney eliminated the drug (fig 4). The upper two scintiscans show nothing at 4 hours. Later, at 21 hours, a round spot can be seen from both the front view (left) and the back view (right). The right lower view of figure 4 is a reduction of figure 3. The left lower view shows the concentration of the drug in the kidney.

Case No. 3.—Patient No. 3 was a 43-year-old man with chronic pneumonitis of the anterior part of the left lower lobe, with suspicion of cancer (fig 5). The bleomycin-cobalt 57 test was negative (fig 6). After a lobectomy was performed, no malignant tissue was found in the removed lobe.

There are strong objections to the use of the cobalt 57 isotope which has a half-life of about 280 days. Eighty percent of this radioactive element is undoubtedly eliminated very rapidly through the kidneys, and only 20% (or 300 rads) is retained. The eliminated effluence is very dangerous if, for example, the urine vessel is broken, and if the effluence is drained into rivers. For that reason, our team has given up the use of the cobalt 57 isotope. We are experimenting with cobalt 55 which has a much shorter half-life. The following cases were treated with cobalt 55.

Case No. 4.—Patient No. 4 was a 63-year-old man with primary epidermoid left apex cancer (fig 7). The drug, marked with cobalt 55, concentrated in the upper lobe and invaded the lymph nodes (fig 8). The localization was progressive, as shown in figure 9, from left to

[1] Department of Surgery, Centre du Chirurgie Thoracique du Val d'Or, Saint Cloud, France.

right at 1, 3, and 7 hours (fig 9). Many other marking isotopes (such as tallium and carbon 14 and 11) have been used in experiments with anticancer drugs.

Case No. 5.—Patient No. 5 was a 57-year-old man with secondary cancer of the right lower lobe (fig 10). Figure 11 shows four scintiscans taken frontward, like a standard X-ray film, using a scintiscan with a gamma camera after an injection of 3 millicuries of copper 67 isotope. An abnormal round opaque area was seen in the right lower part of the scintiscan, just over the liver. The liver opacity was normal. The isotope was eliminated by the liver and the kidneys. We cannot explain the mediastinal opacity; perhaps the lymph nodes had been invaded.

COMMENTS

The use of isotopes to mark different chemotherapeutic drugs has opened a new way of research. We are uncertain of the localization of the drugs on the organs and tissues. We can try, with marked therapeutic drugs, to localize the fixation of these elements and perhaps determine how long the drugs remain in the localized area. Consequently, this procedure could be an aid to better therapeutics.

When asked how to evaluate the efficacy of chemotherapy, we cited the following case as an example.

Case No. 6.—Patient No. 6 was a 39-year-old man with oat cell carcinoma. On the first X-ray film (fig 12), a dark round cancerous opacity can be seen in the field of a large atelectatic opacity (Oct 14, 1966). On the scintiscan of October 21, 1966 (fig 13), 15 mg of mercury (1500 curies of mercury 197) show a round area of fixation. The patient was given 800 mg of cyclophosphamide [2] subcutaneously once a week for 17 weeks. Figure 14 shows a diminution of the opacity, and figure 15 shows a longer fixation of mercury 197.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate.

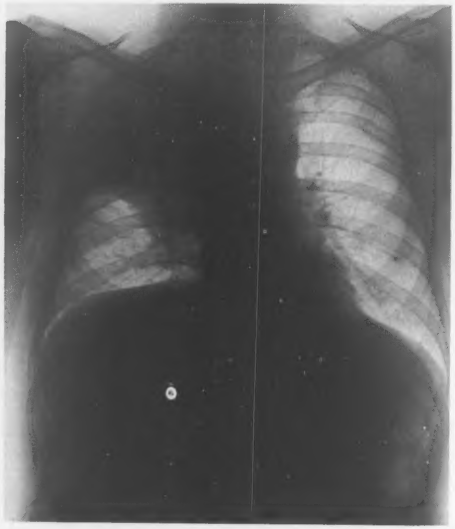

FIGURE 1.—Roentgenogram of patient No. 1 who had adenocarcinoma of the right upper lobe and primary cancer of the pancreas.

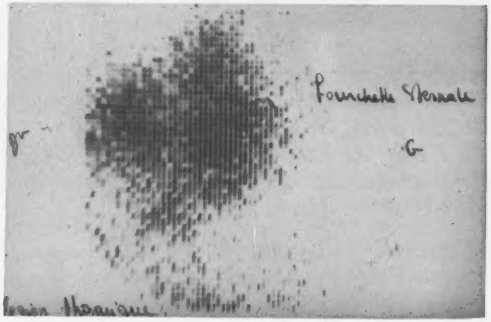

FIGURE 2.—Scintiscan of patient No. 1. Fixation (at 4 hours) of bleomycin labeled with cobalt 57.

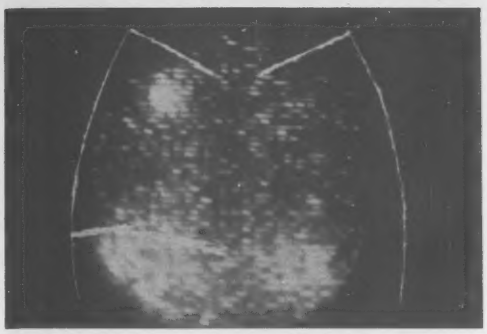

FIGURE 3.—Test (positive) for bleomycin labeled with cobalt 57 in patient No. 2.

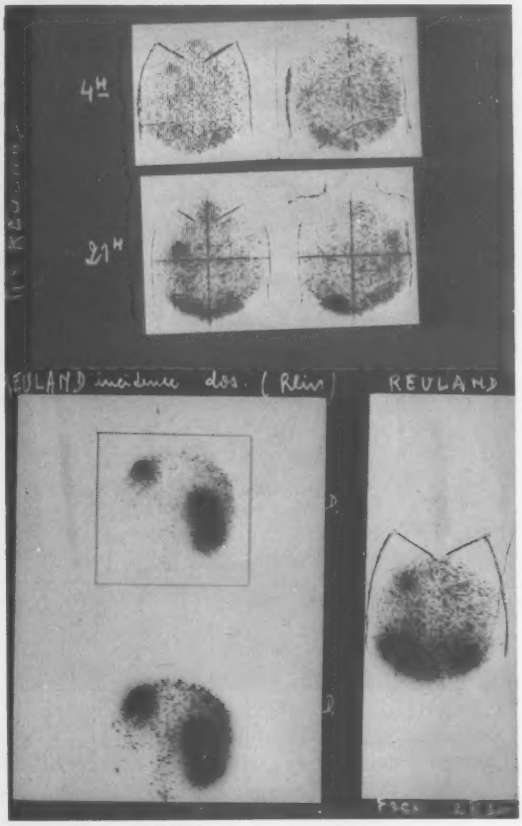

FIGURE 4.—Top: Scintiscans of patient No. 2 at 4 and 27 hours, front view (*left*) and back view (*right*). *Bottom left*: Concentration of drug in kidney. *Bottom right*: Reduction of figure 3.

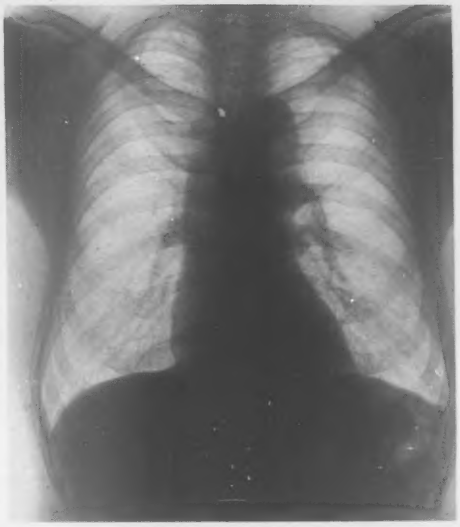

FIGURE 5.—Roentgenogram of patient No. 3 who had chronic pneumonitis of the anterior part of the left lower lobe, with suspicion of cancer.

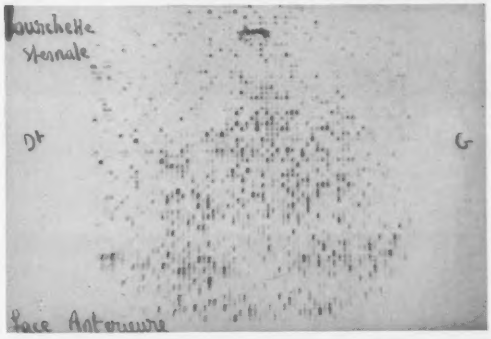

FIGURE 6.—Test (negative) for bleomycin labeled with cobalt 57 in patient No. 3.

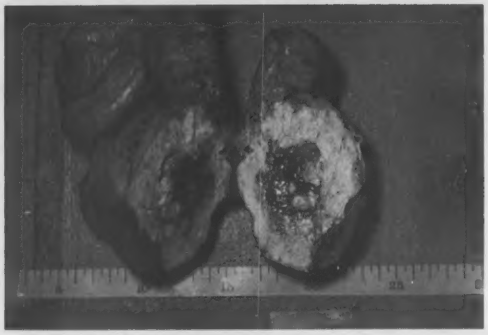

FIGURE 7.—Patient No. 4. Left upper lobe lobectomy.

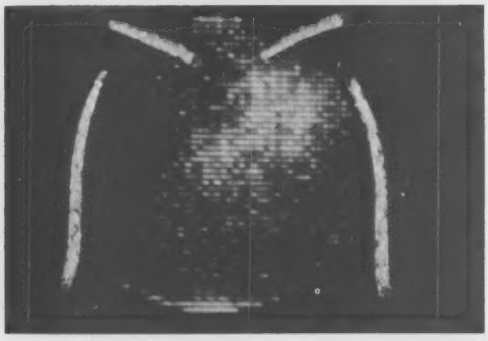

FIGURE 8.—Scintiscan of patient No. 4 showing fixation of bleomycin labeled with cobalt 55.

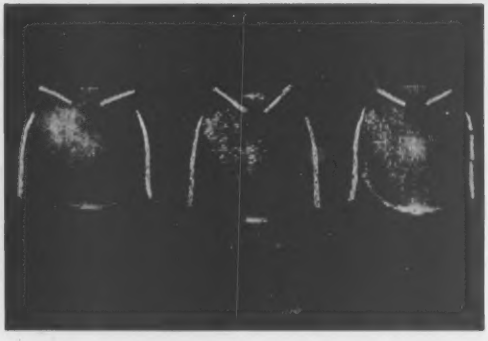

FIGURE 9.—Progressive localization of drug in patient No. 4 at 1, 3, and 7 hours (left to right).

FIGURE 10.—Roentgenogram of patient No. 5 who had secondary cancer of the right lower lobe.

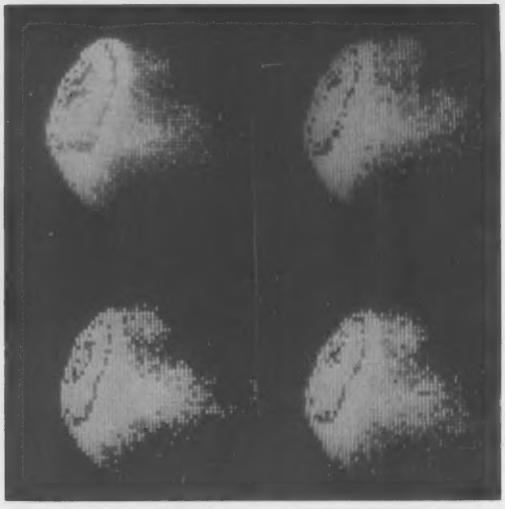

FIGURE 11.—Scintiscans of patient No. 5 at 1, 3, 6, and 24 hours after an injection of 3 millicuries of copper 67 isotope.

FIGURE 12.—Roentgenogram of patient No. 6 who had oat cell carcinoma.

FIGURE 14.—Roentgenogram of patient No. 6 showing diminution of opacity.

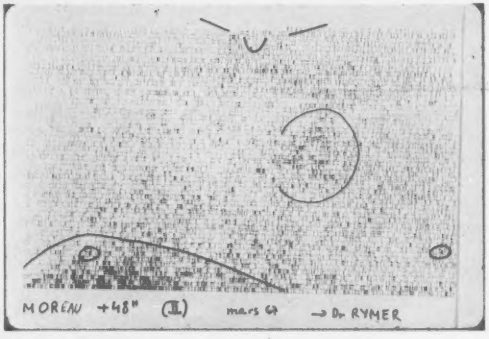

FIGURE 13.—Scintiscan of patient No. 6 after administration of 1500 curies of mercury 197.

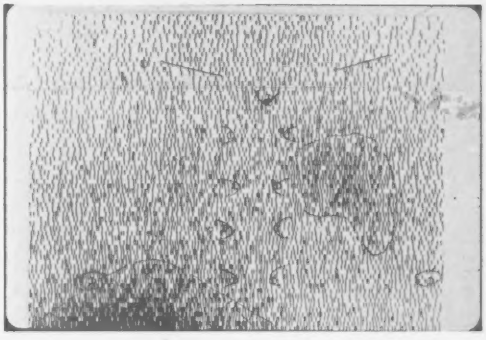

FIGURE 15.—Scintiscan of patient No. 6 showing lower fixation of mercury 197.

Chemotherapy for Lung Cancer at the Institute of Experimental and Clinical Oncology, Academy of Medical Sciences, USSR

N. I. Perevodchikova and M. B. Bychkov [1,2]

From 1960 to 1972 at the Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, chemotherapy was the only method of treatment in 417 patients with inoperable lung carcinoma. Only patients in generally good health and under 70 years of age were included in this study; in addition, all patients were unable to receive surgical or radiation treatment. Biopsies of all tumors were received by a pathologist at our Institute. All drugs were given to toxicity.

The results of chemotherapy for the entire group of 417 patients are presented in table 1. Objective response was registered when chest roentgenograms and tomograms showed a diminution or disappearance of the primary tumor (which was proved by bronchoscopy, if possible) or if the metastatic tumors grew smaller or disappeared. The following definitions of objective response were used: response No. 3 = disappearance of the tumor or its diminution by more than 50% for a period of not less than 1 month; response No. 2 = diminution of the tumor from 25% to 50%; response No. 1 = less than 25% diminution of the tumor. In addition, the survival time of all patients was studied.

Objective responses occurred in patients treated with mechlorethamine (24%), cyclo-

[1] Department of Chemotherapy, Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, Moscow.

[2] We wish to thank Dr. I. G. Olkhovskaya who kindly revised the biopsies of all our patients.

TABLE 1.—Results of chemotherapy for lung cancer

Drug	No. of patients treated	Objective responses				Percent response
		Total	No.— 3	2	1	
Mechlorethamine	98	24	2	10	12	24
Cyclophosphamide	80	18	1	13	4	22
ThioTEPA and other ethylenimines*	58	3	—	1	2	5
1-Methyl-1-nitrosourea	13	7	3	3	1	50
Cyclophosphamide + 1-methyl-1-nitrosourea†	15	4	1	2	1	27
Combination chemotherapy‡	61	12	2	7	3	20
Sarcolysin	19	—	—	—	—	0
Peptides of sarcolysin	23	1	—	—	1	4
Antitumor antibiotics§	33	3	—	—	3	9
Antimetabolites (5-FU and methotrexate)	17	—	—	—	—	0

*Includes benzo-tepa and fluor-benzo-tepa.
†Used only in patients with epidermoid carcinoma.
‡Includes cyclophosphamide, olivomycin A, methotrexate, and 5-FU.
§Includes daunorubicin, olivomycin A, mitomycin C, and chrysomallin.

phosphamide (22%), 1-methyl-1-nitrosourea (50%), and combination chemotherapy (20%).[3] The other drugs given were associated with tumor regression in less than 10% of the cases (thioTEPA and other ethylenimines, 5%; antitumor antibiotics, 9%).

Of special interest from our point of view is the group of patients treated with 1-methyl-1-nitrosourea. This drug proved to be effective in 60% of the patients with undifferentiated (small cell) bronchogenic carcinoma; it was ineffective in the patients with epidermoid carcinoma.[4] Therefore, in table 1 the response rate to 1-methyl-1-nitrosourea in all patients treated at our hospital is 50%. The combination of this drug with cyclophosphamide was effective in 27% of the patients with epidermoid carcinoma. Since cyclophosphamide alone is active in only 9% of the patients with epidermoid carcinoma, we think the combination of the two drugs has a potentiating effect. Preliminary clinical results indicate that there is no cross-resistance between cyclophosphamide and 1-methyl-1-nitrosourea.

Methotrexate and 5-fluorouracil proved to be ineffective in lung cancer; however, we used methotrexate only in cases of epidermoid carcinoma.

Nine combinations of drugs with different mechanisms of action were used in 61 cases of lung cancer. More often, the combination of cyclophosphamide, vinblastine (or vincristine), methotrexate (or 5-FU), and olivomycin A (or chrysomallin or actinomycin D) was used. Relatively more effective were the combinations of cyclophosphamide, vinblastine, and olivomycin A (33% response rate) and cyclophosphamide, vinblastine, olivomycin A, and 5-FU (30% response rate). In two cases the combination of cyclophosphamide, methotrexate, and mitomycin C was effective.

There is a definite correlation between the results of chemotherapy and the histologic type of bronchogenic carcinoma. Therefore, for detailed evaluation of the total group the cases of 100 patients, in whom the diagnosis was not proved by histologic study, were excluded and only 370 cases were evaluated. Among them, epidermoid carcinoma was diagnosed in 120 patients, small cell carcinoma in 80 patients, large cell carcinoma in 8 patients, and adenocarcinoma in 38 patients. In 71 patients the definite type of bronchogenic carcinoma was unspecified.

The results of chemotherapy in relation to histologic structure of bronchial carcinoma are presented in table 2. Chemotherapy proved to be effective in 9% of the patients with epidermoid carcinoma, in 29% of patients with small cell carcinoma, and in 25% of patients with large cell carcinoma; 37 out of 38 patients with adenocarcinoma failed to respond to chemotherapy.

The best results in epidermoid carcinoma were achieved by using the combination of 1-methyl-1-nitrosourea and cyclophosphamide (27% objective response rate); cyclophosphamide was effective in 9% of the patients and mechlorethamine was effective in 6% of the patients. Combinations of drugs other than cyclophosphamide plus 1-methyl-1-nitrosourea proved to be effective in 15% of the patients.

In cases of small-cell carcinoma the most effective drug was 1-methyl-1-nitrosourea (60%–71% objective response rate). Mechlorethamine was active in 48% of the patients, cyclophosphamide in 17%, and combination chemotherapy in 22%.

Survival of patients receiving chemotherapy in relation to the histologic type of bronchial carcinoma is presented in table 3.

The effect of treatment on median survival time in relation to histologic type of bronchogenic carcinoma is presented in table 4.

The median duration of survival in all patients receiving chemotherapy was 6.2 months; in epidermoid carcinoma, 9 months; in small cell carcinoma, 4.8 months; in large cell car-

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

[4] In a study conducted in cooperation with the Institute of Chemical Physics, USSR Academy of Medical Sciences, the response rate in undifferentiated carcinoma to 1-methyl-1-nitrosourea was 71% (17 of 24 patients) (1).

TABLE 2.—Objective responses to chemotherapy in relation to histologic type of bronchial carcinoma

Drug	No. of responders/total No. treated				
	Epidermoid carcinoma (120 cases)	Adeno-carcinoma (38 cases)	Small cell carcinoma (80 cases)	Large cell carcinoma (8 cases)	Bronchogenic carcinoma, unspecified (71 cases)
Mechlorethamine	2/31(6%)	0/6(0%)	10/21(48%)	—	5/8(62%)
Cyclophosphamide	2/23(9%)	0/12(0%)	4/23(17%)	0/1(0%)	3/11(27%)
Ethylenimines	0/6(0%)	0/6(0%)	0/5(0%)	0/2(0%)	1/7(14%)
Sarcolysin and its peptides	0/8(0%)	0/3(0%)	0/6(0%)	0/1(0%)	1/11(9%)
1-Methyl-1-nitrosourea	—	0/1(0%)	3/5(60%)	1/2(50%)	2/5(40%)
1-Methyl-1-nitrosourea + cyclophosphamide	4/15(27%)	—	4/6(67%)	0/1(0%)	1/3(33%)
Antitumor antibiotics	0/8(0%)	0/3(0%)	0/4(0%)	—	1/8(12%)
Antimetabolites	0/10(0%)	0/3(0%)	0/1(0%)	—	0/2(0%)
Combination chemotherapy	3/19(15%)	1/4(25%)	2/9(22%)	1/1(100%)	2/16(12%)
Total	11/120(9%)	1/38(2.6%)	23/80(29%)	2/8(25%)	16/71(22.5%)

TABLE 3.—Survival of patients receiving chemotherapy in relation to histologic type of bronchial carcinoma

Cell type	Percent of patients surviving at—			
	3 mos	6 mos	12 mos	>24 mos
Epidermoid carcinoma	72	43	17	5
Adenocarcinoma	48	34	11	5
Small cell carcinoma	62	30	6	1
Large cell carcinoma	80	25	—	—
Bronchogenic carcinoma, unspecified	75	40	14	2

TABLE 4.—Effect of treatment on median survival time in relation to histologic type of bronchial carcinoma

Cell type	No. of patients	No. and percent of responders	Median survival time (mos)		
			All patients	Responders	Nonresponders
Epidermoid carcinoma	120	11(9%)	9	12	6
Adenocarcinoma	38	1(2.6%)	4.5		
Small cell carcinoma	80	23(30%)	4.8	6.7	2.9
Large cell carcinoma	8	2(25%)	6	7.5	4
Unspecified bronchogenic carcinoma	71	16(22.5%)	6.7	7.4	6
Total	317	53(17%)	6.2	8.7	5

cinoma, 6 months; and in adenocarcinoma, 4.5 months.

Median survival time was 8.7 months in patients responding to chemotherapy and 5 months in patients treated without effect. Patients with epidermoid carcinoma who had positive results lived twice as long (12 months) as patients treated without effect (6 months).

Patients with small cell carcinoma showed a definite correlation between response and survival: median survival was 6.7 months in responders and 2.9 months in nonresponders.

The adenocarcinoma group included 38 patients but it is impossible to draw conclusions on their median survival time in relation to response because practically all the results of chemotherapy in this group were negative.

The experience of the Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, in the use of combination chemotherapy and radiation therapy was presented by M. M. Nivinskaya and coworkers at the Second All-Union Cancer Congress, September 1972. The combination of radiotherapy and a single drug (cyclophosphamide, 5-FU, methotrexate, or chrysomallin) was used in 545 patients with lung cancer. Radiotherapy was given either in one course, with a total dose of 5000–6000 rads over 5–7 months (237 patients), or in a split course (two courses of 3000 rads each every 3 weeks with a 4-week interval between courses).

The combination of radiotherapy with cyclophosphamide, 5-FU, and chrysomallin did not improve the results of treatment. Relatively better results were achieved when a split course of irradiation was combined with methotrexate. The experience with this combination at the Chemotherapy Department of the Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, shows that objective response was achieved in 17 of 25 patients (64%). Therefore, the All-Union Cancer Chemotherapy Center organized a cooperative study with the participation of seven oncologic centers.

In this cooperative study, the following two programs were compared: (*a*) Radiation therapy (200 rads every day for 5 days each week, total dose 3000 rads) combined with methotrexate (2.5 mg orally every day) starting 5 days before radiation therapy. After 4 weeks the course was repeated. (*b*) Radiation therapy as in (*a*) combined with methotrexate (2.5 mg orally daily) and actinomycin D (0.5 mg twice weekly). Two days before the course of radiation, 5-FU was given intravenously (750 mg daily). A second course was given after a 4-week interval.

The results of chemotherapy for lung cancer still remain unsatisfactory. The drugs most active in this type of tumor (among those studied) are cyclophosphamide, mechlorethamine, and 1-methyl-1-nitrosourea. Results of chemotherapy are related to the histologic type of lung cancer: most sensitive to chemotherapy is the small cell carcinoma and far less sensitive is epidermoid carcinoma. Adenocarcinoma practically never responds to chemotherapy. However, the clinical improvement which can be achieved with the most active drugs in 17%–60% of the cases of small cell lung carcinoma is, as a rule, short-lived and the remission, even if all clinical symptoms temporarily disappear, is not longer than 3–6 months.

Although the median survival in patients responding to chemotherapy is longer than in those not responding, their median survival time in general is shorter than in epidermoid carcinoma. The most active combination in epidermoid carcinoma was 1-methyl-1-nitrosourea and cyclophosphamide which produced a clinical effect in 27% of the patients. As a rule, the remissions were short-lasting but the median survival time in patients responding to chemotherapy was two times longer than in patients not responding (12 and 6 months respectively).

As yet, combinations of drugs with different mechanisms of action have not improved the results of chemotherapy. The most promising combination of those being studied is 1-methyl-1-nitrosourea and cyclophosphamide, which proved to be more active in cases of epidermoid carcinoma than either of these agents used alone.

The attempts to combine chemotherapy with radiotherapy are justified, but before special studies are finished we do not feel able to make any conclusions.

LIST OF COMPOUNDS

Actinomycin D: NSC-3053

Benzo-tepa: diethyleneimino-*N*-benzoylphosphamide

Chrysomallin: mixture of actinomyces: C_1, 20%; C_2, 30%; C_3, 50%

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate; Cytoxan

Fluor-benzo-tepa: diethyleneimino-*N*-para-fluor-benzoylphosphamide

5-Fluorouracil: NSC-19893; CAS reg. No. 51-21-8; 5-FU

Mechlorethamine: NSC-762; CAS reg. No. 55-86-7; diethylamine, 2,2′-dichloro-*N*-methyl-, hydrochloride; nitrogen mustard

Methotrexate: NSC-740; CAS reg. No. 59-05-2; glutamic acid, *N*-[*p*-[[(2,4-diamino-6-pteridinyl)methyl] methylamino]benzoyl]-

1-Methyl-1-nitrosourea: NSC-23909; CAS reg. No. 684-93-5

Mitomycin C: NSC-26980; CAS reg. No. 50-07-7

Olivomycin A: NSC-76411

Sarcolysin: NSC-14210; alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, monohydrochloride, DL-; phenylalanine mustard

ThioTEPA: NSC-6396; CAS reg. No. 52-24-4; phosphine sulfide, tris(1-aziridinyl)-

Vinblastine: NSC-49842; CAS reg. No. 6449-03-2; vincaleukoblastine, sulfate (1:1), monohydrate

Vincristine: NSC-67574; CAS reg. No. 2068-78-2; leurocristine, sulfate (1:1)

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Phase II Study of the Effect of Methyl-CCNU (NSC-95441) on Bronchogenic Carcinoma [1]

Hiroshi Takita, Antonio Brugarolas, Arnold Mittelman, and Ronald Vincent [2]

SUMMARY

Twenty-one patients with inoperable bronchogenic carcinoma were treated with methyl-CCNU. The overall response rate was 19% (more than a 50% regression in the size of the lesion). The response rate was 50% for adenocarcinoma and 10% for squamous cell carcinoma. The higher response rates to methyl-CCNU appear to be related to the better immunologic status of the patients involved. At a dose level of 180 mg/m² (given orally every 6 weeks) methyl-CCNU was less toxic than CCNU.

[Cancer Chemother Rep Part 3, vol 4:257–259, 1973]

Methyl-CCNU is an antitumor agent of the nitrosourea group which was developed by the Southern Research Institute.[3] The effect of methyl-CCNU against the Lewis lung tumor in BDF_1 mice is reported to be far superior to that of BCNU and CCNU.[4] We are reporting our clinical experience with methyl-CCNU in the treatment of patients with inoperable bronchogenic carcinoma.

MATERIALS AND METHODS

Methyl-CCNU was supplied in capsules which contained mannitol and magnesium stearate as bulk and was stored at a temperature of 4 C. The dose level for each patient was 180 mg/m² of body surface area given orally every 6 weeks.

All patients treated with methyl-CCNU had inoperable and histologically confirmed bronchogenic carcinoma. One or more measurable tumor masses were prerequisite for followup study. The patients' ages ranged from 47 to 74 years with a mean of 61 years.

Prior to the therapy, each patient was given a complete physical examination including chest roentgenogram, blood cell count, blood chemistry tests, urinalysis, skeletal survey, and scan of the organs using radioisotopes. Upon admission, the patients were given skin tests with *Candida albicans* extract (Hollister-Stier Laboratories, Spokane, Wash) in a 1:100 dilution of full strength antigen, mumps antigen (Eli Lilly and Company, Indianapolis, Ind), purified protein derivative (Parke Davis and Company, Detroit, Mich), and streptokinase-streptodornase (Lederle Laboratories, Pearl River, NY). Followup after the administration of methyl-CCNU consisted of weekly physical examinations, measurements of tumor masses, chest roentgenograms, blood cell counts, and blood chemistry tests.

The antitumor effect was classified in the following manner: complete response—disappear-

[1] Methyl-CCNU: CAS reg. No. 33073-59-5; urea, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitroso-. Supplied by Dr. Stephen K. Carter, Cancer Therapy Evaluation Branch, Division of Cancer Treatment, National Cancer Institute (NCI).

[2] New York State Department of Health, Roswell Park Memorial Institute, Buffalo.

[3] Broder LE, and Carter SK. Clinical brochure: 1-(2-chlorethyl)-3-(4-methyl-cyclohexyl)-1-nitrosourea (Me-CCNU), NSC-95441. Prepared by the National Cancer Institute, Bethesda, Md, Feb 1972.

[4] BCNU: NSC-409962; CAS reg. No. 154-93-8; urea, 1,3-bis(2-chloroethyl)-1-nitroso-.

CCNU: NSC-79037; CAS reg. No. 13010-47-4; urea, 1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-.

ance of all known lesions; partial response—(two categories) more than a 50% decrease in tumor size, and between 30% and 50% decrease in tumor size; progression—continued growth of the tumor as shown by sequential measurements.

RESULTS

Four of 21 patients (19%) responded to methyl-CCNU. One patient had a complete response and three patients had more than a 50% regression in tumor size. One additional patient had less than a 50% regression.

One of ten patients with squamous cell carcinoma (10%) and three of six patients with adenocarcinoma (50%) responded to methyl-CCNU. None of the five patients with anaplastic carcinoma responded (table 1).

TOXICITY

The most frequently observed side effects were nausea and vomiting in 12 of 21 patients (57%). The onset of the gastrointestinal symptoms was usually 4–6 hours after the drug was administered and the symptoms subsided within 12 hours. Hematologic toxicity was generally mild and was observed between 4 and 6 weeks after the administration of methyl-CCNU. Leukopenia (3000 cells/mm^3) developed in three of 21 patients. Thrombocytopenia (less than 80,000 cells/mm^3) was observed in three of 21 patients. In two of these three patients hemoptysis developed and hospitalization and blood transfusions were required.

The response observed in a patient with squamous cell carcinoma was transient and lasted 12 weeks. The durations of response for the three cases of adenocarcinoma were 17, 20, and 22 weeks respectively, and these patients are still in remission.

Influence of the immunologic status of the patients on their response to therapy was studied by delayed hypersensitivity skin tests. Three of five patients whose diameter of skin test reaction was greater than 1 cm prior to the administration of methyl-CCNU responded to the therapy (60%). Only one of 16 patients with a skin test reaction less than 1 cm in diameter responded to the drug (6.3%) (table 2).

Only one of six patients who had had previous chemotherapy responded to methyl-CCNU. This patient previously received bleomycin (NSC-125066) and had a partial regression of the tumor. No antitumor effect of methyl-CCNU was observed in patients who had previously received hexamethylmelamine and meturedepa (table 3).[5]

DISCUSSION

Other compounds of the nitrosourea group (BCNU and CCNU) have been tested against bronchogenic carcinoma. Olshin et al (1) reported no antitumor effect of BCNU in 25 cases

[5] Hexamethylmelamine: NSC-13875; CAS reg. No. 645-05-6.

Meturedepa: NSC-51325; CAS reg. No. 1661-29-6; carbamic acid, [bis(2,2-dimethyl-1-aziridinyl) phosphinyl]-, ethyl ester; AB-132.

TABLE 2.—Response to therapy according to skin test reaction

Diameter of skin test reaction	No. of patients tested	No. of responses (%)
<1 cm	16	1 (6.3)
>1 cm	5	3 (60)

TABLE 1.—Response to methyl-CCNU according to cell type

Cell type	No. of patients treated	No. of patients responding with regression			No. of patients with progression	Response rate (%)
		100%	>50%	<50%		
Squamous cell carcinoma	10	0	1	1	8	10
Adenocarcinoma	6	1	2	0	3	50
Anaplastic carcinoma	5	0	0	0	5	0
Total	21	1	3	1	16	19

TABLE 3.—Influence of previous treatment

Previous chemotherapy	No. of patients treated	No. of patients with— Response	Progression
Hexamethyl-melamine	2	0	2
Meturedepa	3	0	3
Bleomycin	1	1	0
Total	6	1	5

of bronchogenic carcinoma. Ahmann et al (2) noted three responses (12%) among 25 patients with bronchogenic carcinoma treated with BCNU. We previously observed an 18% response rate in 50 patients with bronchogenic carcinoma treated with CCNU (3).

Although the number of patients treated with methyl-CCNU is not large enough to be conclusive, it appears that both methyl-CCNU and CCNU are almost equally effective against bronchogenic carcinoma. In our previous paper on CCNU (4) we discussed the effect of the immunologic status of the patients on the response to chemotherapy. None of 18 anergic patients responded, while six of 17 patients who had had a good reaction to the delayed hypersensitivity skin tests responded to CCNU. With methyl-CCNU we observed similar findings. Only one of 16 anergic patients responded, while three of five patients with good skin test reactions responded to methyl-CCNU.

The toxicity of methyl-CCNU was similar to that of CCNU, but the hematologic toxicity of methyl-CCNU was found to be less than that of CCNU (table 4) (4). In our series we used a

TABLE 4.—Comparison of the toxic effects of methyl-CCNU and CCNU

Toxic effect	No. of patients with toxic effects/total No. treated Methyl-CCNU*	CCNU†
Nausea and vomiting	12/21 (57%)	32/50 (64%)
White blood cell count <2000 cells/mm³	0/21 (0%)	3/50 (6%)
Platelet count< 80,000 cells/mm³	3/21 (14%)	12/50 (24%)

*Methyl-CCNU = 180 mg/m² every 6 weeks.
†CCNU = 130 mg/m² every 6 weeks.

dose schedule of 180 mg/m² of methyl-CCNU every 6 weeks, but probably a slightly higher dose schedule (200–220 mg/m²) should be tried. With a higher dose schedule, a better antitumor effect can be obtained with methyl-CCNU than with CCNU.

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Clinical Evaluation of an Innoxious Antineoplastic Agent: Preliminary Study of 106 Patients Treated With or Without RSV After Pulmonary Resection for Bronchogenic Carcinoma [1]

Jens L. Hansen [2]

SUMMARY

A series of 106 consecutive patients with bronchogenic carcinoma were treated postoperatively with RSV or placebo for 4 months. At followup, 6–18 months after surgery, the results in the RSV-treated group appeared to be better than those in the placebo group.

[Cancer Chemother Rep Part 3, vol 4:261–264, 1973]

RSV consists of two substances, 1,2-diphenyl-$\alpha\beta$-dicetone and its superoxide. It has been widely used experimentally [3] and in veterinary medicine in the treatment of virus infections and neoplastic diseases. Histologically, RSV regularly causes devitalization, necrosis, karyolysis, and pyknosis in diseased cells. The same effects are reported in cells from human carcinoma of the uterine cervix. Clinical pathologic results of RSV in man have not yet been reported and no controlled clinical research studies have been published.

I have used RSV for more than 2 years,[4] mostly as an antineoplastic agent. Initially, inoperable patients were treated. In a few instances, a surprisingly long survival time occurred. The dosage was, and still is, arbitrary. Twelve doses a day orally for 4 months were given in most cases. No side effects were noted. Careful and regular analysis of blood, liver, kidneys, and other organs revealed no pathologic changes caused by the treatment.

A clinical study was planned in patients who had received pulmonary resection for bronchogenic carcinoma. RSV or a placebo of identical appearance was to be given at random. At followup, code numbers would reveal what the individual patient had received. Until then, nobody in the hospital, distributing link, or factory knew which patients received the drug.

RSV

RSV was introduced in 1967 in Madrid, Spain, by Ramón, Sanz, and de la Vega. Their primary intention was to treat viral diseases. In animal experiments, during which they used high-power microscopy, ultrastructural cellular changes were discovered that indicated a possible antineoplastic effect of the agent. The active substances are insoluble in water, alcohol, and ether and can be administered only in lipid vehicles or ethyl oleate.

For treatment in man, each "fat cartridge" contains 0.032 g of 1,2-diphenyl-$\alpha\beta$-dicetone and 0.016 g of 1,2-diphenyl-$\alpha\beta$-dicetone superoxide. Usually, 12 doses a day are given orally,

[1] RSV: 1,2-diphenyl-$\alpha\beta$-dicetone and 1,2-diphenyl-$\alpha\beta$-dicetone superoxide. RSV and placebo were obtained from Laboratories LEO, S.A. de Compania Ibero Danese, Madrid, Spain, through Valentin Aage Moller and Co., Copenhagen, Denmark.

[2] Department of Thoracic Surgery, University of Copenhagen, Bispebjerg Hospital, Denmark.

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for a total daily intake of about 10 mg/kg of body weight.

No side effects have been observed in laboratory animals or man. Some patients have been treated for more than 3 years. Further details were published, probably for the first time in the English literature, by Ramón, Sanz, and de la Vega, at the Fifth International Pharmacological Congress, San Francisco, California, in 1972.

RSV for Bronchogenic Carcinoma

For 15 months (from April 1, 1971) RSV or placebo was given to all patients surviving pulmonary resection for bronchogenic carcinoma. The treatment started a few days after surgery and was continued until the amount delivered from the hospital had been taken. Twelve doses a day was the recommended dosage and the treatment took 4 months. Some patients received a slightly smaller daily dose, thus prolonging the treatment to about 5 months.

During the first 12 months, the treatment was given to 115 patients, but in nine patients treatment was interrupted because of general malaise due to cancer or psychological reasons. In 106 patients, the therapy was carried out according to plan; in the patients who died, therapy was given until shortly before death.

During followup examinations (given regularly once a month in the outpatient clinic), clinical, laboratory, and radiologic examinations were done and the intake of medicine was registered. Preliminary results were noted 6–18 months postoperatively (average, 12 months). At that time the treatment codes showing which patients belonged to the treated group and which belonged to the control group were revealed. (Twelve patients who died within 4 weeks are excluded from any of the figures mentioned in this paper. This is true whether or not they had originally been included in the research.)

Fifteen women and 91 men were included in the series, as shown in table 1. From the table it appears that the age distribution is somewhat different from most other series of patients with resectable bronchogenic carcinoma because of a high proportion of elderly patients. No less than 65% were 60 years of age or older.

In table 2 the histologic types are analyzed. Epidermoid (planocellular) carcinoma dominates (53%). Low differentiated epidermoid cancers add a further 6% to this figure. Adenocarcinoma was present in 18% and small cell anaplastic (oat cell) carcinoma in 10% of the resectable patients. The remaining 13%

TABLE 1.—Age and sex distribution of patients with bronchogenic carcinoma treated postoperatively with RSV or placebo

	No. of patients receiving—		Total No. of patients
	RSV	Placebo	
Men	45	46	91
Women	6	9	15
Age (yrs)			
≤49	5	4	9
50–59	14	14	28
60–69	26	29	55
≥70	6	8	14
Total	51	55	106

TABLE 2.—Histologic types of bronchogenic carcinoma in patients treated postoperatively with RSV or placebo

Histologic type	No. of patients receiving—		Total No. of patients
	RSV	Placebo	
Epidermoid	27	29	56
Epidermoid, low differentiated	3	3	6
Small cell anaplastic	5	6	11
Adenocarcinoma	10	9	19
Others	6	8	14
Total	51	55	106

had various other types or mixed tumors containing elements of more than one malignant cell type.

Table 3 shows the surgical procedures used and the degree of radicality of the operation. Of course, the surgical interventions had many variations. Several of the pneumonectomies were extended, not only by deep mediastinal dissection and/or pericardiotomy, but also by resection of trachea, left auricle, thoracic wall, etc. Lobectomy included bilobectomy and bronchial sleeve resection, as well as a few segmentectomies. Pneumonectomy and lobectomy were each performed in 53 patients in the series. Radical removal of the malignant tumor was performed in approximately half the pneumonectomies and in almost all the lobectomies. Frozen section microscopy was used in all operations to ensure the highest possible degree of radicality.

An operation was considered radical when no metastases were found and when no disease was disclosed in the bronchial stump, pleural lining, chest wall, or other regions accessible to the surgeon.

RSV was given at random to 51 patients and placebo was given to 55 patients. The treated and control patients were equally represented in the subdivisions of the total series.

RESULTS

Analysis of the chemotherapy course 6–18 months (average, 12 months) after pulmonary resection for bronchogenic carcinoma is shown in table 4. The results are termed "poor" in

TABLE 3.—Types of surgery and degree of radicality in patients with bronchogenic carcinoma treated postoperatively with RSV or placebo

Degree of radicality	Type of surgery	No. of patients receiving—		Total No. of patients
		RSV	Placebo	
Radical	Pneumonectomy	11	13	24
	Lobectomy	21	24	45
	Total	32	37	69
Nonradical	Pneumonectomy	13	16	29
	Lobectomy	6	2	8
	Total	19	18	37
Radical and nonradical	Pneumonectomy	24	29	53
	Lobectomy	27	26	53
	Total	51	55	106

TABLE 4.—Preliminary followup results (6–18 months after treatment) in patients with bronchogenic carcinoma treated postoperatively with RSV or placebo

Degree of radicality	Type of surgery	No. of patients receiving—				Total No. of patients	
		RSV		Placebo			
		Good response	Poor response	Good response	Poor response	Good response	Poor response
Radical	Pneumonectomy	9	2	8	5	17	7
	Lobectomy	19	2	19	5	38	7
	Total	28	4	27	10	55	14
Nonradical	Pneumonectomy	8	5	7	9	15	14
	Lobectomy	5	1	2		7	1
	Total	13	6	9	9	22	15
Radical and nonradical	Pneumonectomy	17	7	15	14	32	21
	Lobectomy	24	3	21	5	45	8
	Total	41	10	36	19	77	29

all patients who died from or with cancer and in all living patients with confirmed or strongly suspected metastases. The remaining patients are clinically and radiologically well, and no laboratory signs of cancer have been found. They represent the good results.

During the observation period nine patients died. Two of them had been treated with RSV—one with the total dosage and one with less than half the total dosage. Seven of the control patients died—five from cancer. Autopsy was done in all cases but one.

Table 4 shows that poor results were registered in ten of 51 RSV-treated patients (19.6%) and in 19 of 55 placebo-treated patients (34.6%). The same tendency to improved results in the treated group is seen in the other data in the table. However, no statistically significant difference between the treated and untreated groups can be demonstrated.

COMMENTS

The rather high average age in the series is partly explained by the general age distribution of the population served by the department, mainly the city of Copenhagen, where the number of people 60 years of age and older is double that in the surrounding districts. Previous experiences (1) have shown that even in the higher age groups, satisfactory results may be obtained. The age distribution seen here will make the outlook graver but does not prevent comparison between a treated and a control group.

The histologic typing of bronchogenic carcinoma is according to the World Health Organization nomenclature. Patients with questionable diagnoses have been discussed at clinicopathologic conferences, especially those with highly malignant tumors found to be without metastases or to survive for more than 1 year. In a few patients the original diagnosis has been revised.

The various factors influencing the course after surgery (age, histologic type, surgical procedure, and radicality of the intervention) seem to weigh equally on the two groups compared in this study. The rather uniform tendency to improved results in the treated group may, in spite of the lack of statistical significance, be explained by an antineoplastic effect of RSV.

In a previously published series from the department (2), the 1-year survival rate after surgical treatment of bronchogenic carcinoma was 65%. This figure is very near the survival rate noted in the placebo-treated patients in the present series and lower than the survival rate noted in the RSV-treated patients (80%).

It should be stressed that the dosage of RSV was arbitrary. Although the daily dose of 12 rather large "fat cartridges" is probably as high as patients can be expected to take, the duration of treatment may easily be prolonged, possibly with improved results.

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Bronchogenic Carcinoma: New Drugs Available for Study

Milan Slavik and Stephen K. Carter [1]

SUMMARY

Bronchogenic carcinoma is considered one of the "signal" tumor types in which new antineoplastic drugs sponsored by the Division of Cancer Treatment, National Cancer Institute, are tested. Among the new drugs which have completed phase I evaluation and are ready for pnase II study in bronchogenic carcinoma are *cis*-diamminedichloroplatinum, isophosphamide, and 5-azacytidine. Chromomycin A_3 has entered phase I studies. Preclinical and clinical data on these drugs with respect to bronchogenic carcinoma are discussed.

[Cancer Chemother Rep Part 3, vol 4:265–269, 1973]

One of the important functions of the Division of Cancer Treatment, National Cancer Institute, is the sponsoring of new anticancer drugs for clinical trial. All of these drugs are tested in bronchogenic carcinoma, which is considered one of the Program's "signal" tumor types.

Among the drugs which have recently completed phase I evaluation and are ready for phase II study in this disease are *cis*-diamminedichloroplatinum, isophosphamide, and 5-azacytidine.[2] The last drug which will be discussed, chromomycin A_3, has recently entered phase I studies.

Cis-diamminedichloroplatinum (fig 1) is one of a group of platinum compounds first noted to have antibiotic effect by Rosenberg and his colleagues in 1965 (1). Since then they have been found to possess antitumor activity in animals (2–4). The drug has been selected for clinical study because of its activity against the L1210 leukemia system, where it has shown significant activity over a variety of dose schedules when given intraperitoneally. When the drug is given orally, there is no activity. Pharmacokinetic studies in man have revealed that platinum is rapidly removed from the circulation and widely distributed in the tissues; less than 10% of the platinum remains in the plasma at 1 hour (5). The initial half-life ranges between 41 and 49 minutes, while the secondary half-life ranges between 58.5 and 73 hours (6). About 90% of the drug in plasma appears to be protein bound; 19.2%–33.9% of the administered drug is excreted in the urine within 24 hours and 25%–43.6% is excreted in 96 hours (6).

Clinically, the drug has been used in phase I trials with various dose schedules: single intravenous (iv) dose (6,7) repeated every 3 weeks (7), twice weekly iv doses repeated every 3–4 weeks (8), daily iv doses given for 5 days repeated every 3 weeks (7,8), and daily doses given by iv push until toxicity occurs (9).

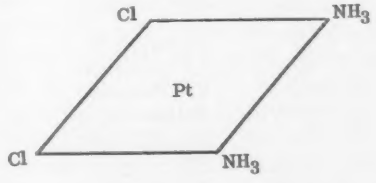


FIGURE 1.—Structure of *cis*-diamminedichloroplatinum.

[1] Cancer Therapy Evaluation Branch, Division of Cancer Treatment, National Cancer Institute (NCI), Bethesda, Md.

[2] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

The toxicity reported in these studies (6–9) includes predictable reversible myelosuppression, reversible renal insufficiency, high frequency ototoxicity detectable by audiometry, and gastrointestinal intolerance.[3]

For phase II clinical studies in bronchogenic carcinoma, we recommend the following dose schedules: 40 mg/m² as a single iv injection or 15–20 mg/m²/day × 5, both repeated every 3 weeks. These dose schedules are based on an analysis of the data from phase I studies.

Isophosphamide is an analog of cyclophosphamide which was investigated because of superior cytostatic activity in the L1210 leukemia system. Table 1 compares the structures and L1210 activity of isophosphamide with those of cyclophosphamide and another analog, NSC-109723. Besides the superiority to cyclophosphamide in L1210, activity for isophosphamide has also been noted in Lewis lung carcinoma, Ehrlich ascites tumor, and Yoshida sarcoma. The initial investigation of isophosphamide was sponsored by the Asta-Werke Chemical Company, Germany (10–15), and extensive trials have been carried out by German investigators. Isophosphamide appears to have many characteristics in common with cyclophosphamide, including the following: toxic effects (dose-related effects, reversible leukopenia with relative platelet sparing, nausea, and cystitis), forms of administration (iv or oral), and range of tumor activity in man. Preliminary German studies as well as South African studies (16) with single high-dose therapy repeated every 4 weeks have reported activity in bronchogenic carcinoma, particularly in small cell tumors.

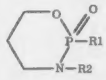
Phase I studies in this country have been conducted by Dr. Cohen in the NCI-VA Medical Oncology Service,[4] and in these studies the maximal tolerated single iv dose was over 5000 mg/m². His recommended dose for phase II clinical trials ranges between 3800 and 5000 mg/m². Phase II studies with doses in this range have already been started in some signal tumors.

5-Azacytidine is an anticancer drug of Czechoslovakian origin (17); its structure is shown in figure 2. Evidence indicates that it acts as an analog of cytidine and is therefore incorporated into both RNA and DNA. By disrupting the processes of nucleic acid sequences

[3] Goldsmith MA, Broder LE, and Carter SK. Clinical brochure: *cis*-platinum (II) diamminedichloride, 1972. Prepared by the NCI, Bethesda, Md.

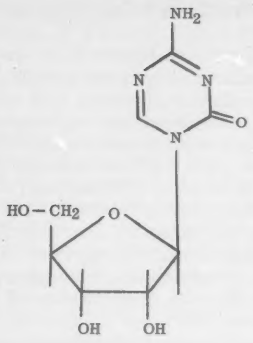
[4] Cohen MH. Personal communication, 1972.

TABLE 1.—Relative effectiveness against L1210 ascites



Treatment		Cyclophosphamide R1=N(CH₂CH₂Cl)₂ R2=H		NSC-109723 R1=N(CH₂CH₂Cl)₂ R2=CH₂CH₂Cl		Isophosphamide R1=NCH₂CH₂Cl R2=CH₂CH₂Cl	
Route	Schedule	ILS (%)*	Optimal dose	ILS (%)*	Optimal dose	ILS (%)*	Optimal dose
Ip	Once, Day 1	>300	(180)	>300	(500)	>300	(300)
Ip	Q3h, Day 1	150	(300/8)	>300	(300/8)	120	(300/8)
Ip	Qd, Days 1–9	50	(39)	95	(39)	50	(65)
Ip	Qd, Days 1,5,9	70	(108)	135	(65)	85	(39)
Ip	Q3h, Days 1,5,9	60	(108/8)	145	(180/8)	110	(180/8)
Ip	Qd, Days 1,9	120	(108)	>300	(300)	125	(180)
Ip	Q3h, Days 1,9	70	(180/8)	100	(180/8)	155	(300/8)
Oral	Once, Day 1	153	(300)	>300	(180)	>300	(500)
Oral	Qd, Days 1,9	100	(108)	>300	(500)	>300	(500)

*ILS (%) = percent increase in survival time over controls.



Active System: Leukemia L1210 (daily schedule most active)

Mechanism of Action: Inhibits DNA, RNA, and protein synthesis. Acts as analog of cytidine and is incorporated into DNA and RNA. Disrupts the process of translation of nucleic acid sequences into protein.

FIGURE 2.—Structure and basic information for 5-azacytidine.

into protein, the synthesis of protein is inhibited (17–26). It was selected for clinical trial on the basis of its activity against mouse L1210 leukemia.

Pharmacokinetic studies in man have shown the plasma half-life after iv administration of the drug to be 3.5 hours, 85% radioactivity being excreted within 48 hours (27). Phase I clinical studies have been performed in a variety of institutions. The maximally tolerated dosages appear to be 533 mg/m² (iv single weekly dose),[5] 160–200 mg/m² daily × 5 repeated every 3 weeks (28), and 1.6 mg/kg (60 mg/m²) given iv daily for 10 days (29). The toxicity observed consists mainly of nausea and vomiting, which can be quite severe, and marrow suppression. Activity has been reported in breast cancer, malignant melanoma, and acute myelocytic leukemia. Clinical trials are now in progress which include bronchogenic carcinoma.

Chromomycin A_3 (fig 3) is an anticancer antibiotic of Japanese origin isolated from a

[5] Unpublished data of the Eastern Cooperative Oncology Group (with the permission of the Group Chairman, Dr. Paul Carbone).

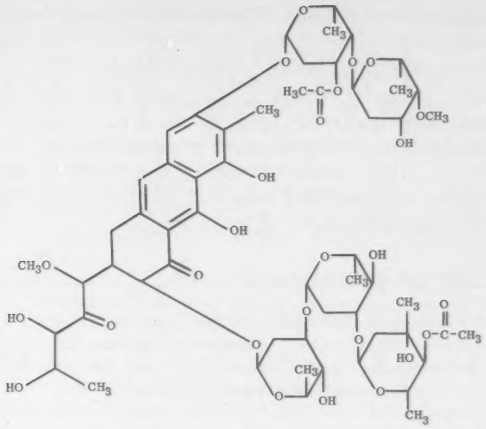


FIGURE 3.—Structure of chromomycin A_3.

culture of *Streptomyces griseus* No. 7 (30). It is commercially available in Japan as "toyomycin." The mechanism of action of chromomycin A_3 has been described as inhibition of DNA-dependent RNA synthesis (31–34). The drug has been selected for clinical trials on the basis of its activity against P388 leukemia in mice, where it has shown superiority to mithramycin and was schedule dependent. Cytostatic activity has been reported also in a number of experimental animal tumors such as Yoshida sarcoma, Sarcoma 180, Ehrlich ascites, and others (35). In preclinical pharmacokinetic studies, the drug has been found to be rapidly excreted in the bile and urine and almost totally cleared from the plasma 3 hours after iv injection (36).

To date, chromomycin A_3 has had clinical trial in Japan and South Africa in more than 500 patients with a wide variety of neoplastic diseases. The toxic effects include nausea and vomiting after daily doses of 1 mg and higher (37,38). Moderate leukopenia has been reported (37–39), the white bood cell count being less than 3000 cells/mm³ in only 6% of the patients (39). Local pain, induration, and necrosis have been reported at the injection site after extravascular administration. Clinically, the drug has already been used in combination with radiotherapy (38–40) and in combination with alkylating agents, where it has shown a syner-

gistic effect (41,42). Responses in bronchogenic carcinoma have been reported both in the Japanese and South African studies (37,38, 43). Recently, the drug has been approved as an investigational drug in the United States, and phase I clinical studies sponsored by the DCT, NCI, are progressing to establish the maximum tolerated dose and further define the toxicity parameters of the drug.

LIST OF COMPOUNDS

5-Azacytidine: NSC-102816; CAS reg. No. 320-67-2; *s*-triazin-2(1*H*)- one, 4-amino-1-β-D-ribofuranosyl-

Chromomycin A_3: NSC-58514; CAS reg. No. 7059-24-7

***Cis*-diamminedichloroplatinum:** NSC-119875

Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, monohydrate

Isophosphamide: NSC-109724; CAS reg. No. 3778-73-2; 1,3,2-oxazaphosphorine, 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-, 2-oxide

NSC-109723: 1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]-3-(2-chloroethyl)tetrahydro-, 2-oxide

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Aspects of the Immunologic Treatment of Lung Cancer

G. Alth,[1] H. Denck,[1] M. Fischer,[1] K. Karrer,[2] O. Kokron,[1] E. Korizek,[1] M. Micksche,[2] E. Ogris,[1] C. Reider,[2] R. Titscher,[1] and H. Wrba[2]

SUMMARY

From October 9, 1970, to May 11, 1971, 57 patients with inoperable bronchogenic carcinoma were included in a pilot study undertaken jointly by the Lainz Hospital and the Institute for Cancer Research of the University of Vienna, Austria. Patients were randomized into one of five groups: Group I (polychemotherapy), included nine patients of whom one is alive 20 months after treatment; Group II (vitamin A plus cyclophosphamide), included 15 patients of whom two are alive 20 and 23 months after treatment; Group III (vitamin A and proteolytic enzyme treatment), included 15 patients of whom two are alive 22 months after treatment; Group IV (vitamin A, proteolytic enzyme, and cyclophosphamide), included ten patients, none of whom are surviving; Group V (immunotherapy with aqueous pooled bronchogenic carcinoma extract), included eight patients of whom two are alive 19 and 22 months after treatment.

[Cancer Chemother Rep Part 3, vol 4:271–274, 1973]

Because we have accumulated very little data from this study, our report is primarily intended to stress the need for cooperative work and for new forms of treatment of inoperable bronchogenic carcinoma.

Since 1970, a cooperative study has been undertaken in accordance with the principles laid down by the International Union Against Cancer for controlled clinical trials (Technical Reports, series 7). Patients with inoperable bronchogenic carcinoma admitted to one of the largest clinics in Vienna were included in a prospective controlled study and submitted to an alternate treatment schedule.

The first patient was admitted on October 9, 1970. Prerequisites for inclusion in the study were: (*a*) histologic confirmation of carcinoma, (*b*) clinical inoperability, and (*c*) no previous treatment of the neoplasm. No limit was placed on the size of the tumor. The presence of definite extrapulmonary metastases was grounds for exclusion. Only male patients were included.

Patients were divided into five groups according to the principles of randomization. Group I received polychemotherapy consisting of cyclophosphamide (12 mg/kg), 5-fluorouracil (12 mg/kg), methotrexate (0.5 mg/kg), and vinblastine (0.1 mg/kg).[3] Group II received high doses of vitamin A and cyclophosphamide. The high-dose vitamin A therapy consisted of 3,000,000 units daily until the appearance of skin reactions, followed by 30-mg/kg shock doses of cyclophosphamide in 1 week. Treatment was repeated after 6 and 8 weeks. Group III received vitamin A as in the previous group and the proteolytic enzyme preparation Wobe-Mugos in a rectal infusion of 10 ml daily. Group IV received vitamin A, cyclophosphamide, and

[1] Krankenhaus der Stadt Wien Lainz, Vienna, Austria.

[2] Institute for Cancer Research of the University of Vienna, Austria.

[3] Chemical nomenclature, NSC numbers, and CAS registry numbers for all compounds mentioned in this paper are included in the List of Compounds at the end of the text.

Wobe-Mugos as in the previous groups. Group V received a tumor-extract injected subcutaneously twice weekly throughout the study. The tumor-extract was prepared from tumor material removed during operation from at least six bronchogenic carcinomas of various histologic types and from donors of different blood groups. The average weight of the pooled tumor material was 30 g. The material was homogenized in phosphate buffered saline (PBS) (1:2, w/v; 0.03 M PBS, pH 7.3). After removal of cell debris, it was centrifuged at 1000 × *g* and the aqueous supernatant was saved. The pellet was again extracted as before and the supernatant was pooled with the first supernatant and further centrifuged at 22,000 × *g* for 20 minutes. This supernatant was passed through a millipore filter and the protein content was adjusted to 1.5 mg/ml. The sterile extract was then stored in ampules.

The last patient in the study was admitted on May 11, 1971; a total of 57 patients had been included at that date. All patients in the study remained under constant control and were examined and checked every 6 weeks.

It was recognized at the beginning of the pilot study that the small number of patients would allow no definite conclusions to be drawn, and it was intended that this study would serve as the basis for a larger, long-term study. Attempts were therefore made to assess the results as soon as possible after inclusion of the last patient (table 1).

The histologic classification of the tumors is presented in table 1. To assist in the assessment of results, a classification of prognosis factors

TABLE 1.—Histologic types of bronchogenic carcinoma in each group

Histologic type	Group—				
	I	II	III	IV	V
Squamous cell carcinoma:					
with keratinization	2	7	6	4	5
without keratinization	3	1	3	1	—
Large cell carcinoma	1	—	1	—	—
Oat cell carcinoma	1	4	3	2	1
Adenocarcinoma	2	3	2	3	2

TABLE 2.—Prognosis factors

Tumor localization and disease status	Patient status			
	No weight loss, symptom-free	Minimal symptoms, good general condition	Generalized symptoms, physically handicapped	Bedridden
	Prognosis factor			
Technically and medically operable				
Central disease	1	2	3	4
Peripheral disease	5	6	7	8
Technically operable but medically contraindicated: inoperable				
Central disease	9	10	11	12
Peripheral disease	13	14	15	16
Locally and technically inoperable				
Central disease	17	18	19	20
Peripheral disease	21	22	23	24

was drawn up (table 2). The distribution of prognosis factors was approximately equal in all therapy groups but there was an irregular distribution of histologic types because randomization of this parameter had not been taken into consideration.

The results of the pilot study have served as a basis for a prospective study which is now in progress.

The number of patients in each group varied greatly. Group I (polychemotherapy) had nine patients, Group II (vitamin A and cyclophosphamide) had 15, Group III (vitamin A and enzyme therapy) had 15, Group IV (vitamin A, enzyme therapy, and cyclophosphamide) had ten, and Group V (immunotherapy) had only eight. These different numbers are, of course, due to randomization.

The status of all patients on October 8, 1972, was as follows: Of 57 patients a total of 50 had died. In the polychemotherapy group (Group I) one patient was still alive after 20 months. In Group II, after treatment with vitamin A and cyclophosphamide, two of 15 patients were alive after 20 and 23 months. In Group III (treatment with vitamin A and an enzyme preparation) two of 15 patients were alive after 23 and 22 months. In Group IV (combination of vitamin A, enzyme, and cyclophosphamide) no patients had survived, and in Group V (immunotherapy) two of the original eight patients were still alive after 19 and 22 months (fig 1).

It is naturally not possible to draw any conclusions from such a small number of cases. From the attempt at immunotherapy we could draw the subjective inference that in the two patients still alive, no ill effects have resulted. It must be pointed out that the clinicians in our group were very skeptical about our attempts at immunotherapy with tumor antigen, particularly because of the lack of data in this area. At the outset the results were particularly bad, but we persevered with this form of treatment because it could be stated with reasonable certainty that immunotherapy would not intensify the disease. This naturally strengthened our determination and in the main study this form of treatment will be continued.

Important changes in the execution of our current study as compared with the pilot study described in this report will be that the qualifications for inclusion will be more strict. First,

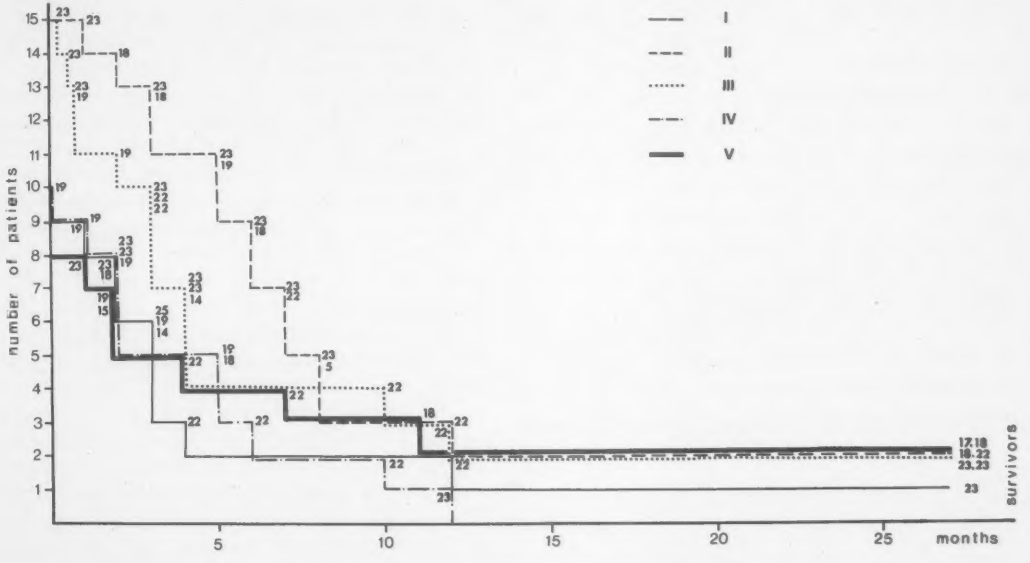

FIGURE 1.—Survival time of patients with inoperable bronchogenic carcinoma treated with various combinations of chemotherapy, immunotherapy, and proteolytic enzyme. (*See* text for definitions of therapy.)

an exact analysis of the extent and size of tumor spread must be undertaken. Still excluded from the study will be previously treated patients, patients with contralateral lung metastases or extrapulmonary metastases, and patients whose tumors have a diameter of more than 8 cm (as shown by roentgenogram).

The immunotherapy begun in the pilot study will continue. The first patient in the new study was admitted in August 1971. Due to the more stringent qualifications for admission there are only 36 patients in the study after a period of 15 months. Every patient will have an immuneprofile carried out before treatment and 14 and 36 days after the start of therapy. Each time the patient is called in for treatment or checkup, usually after 6 weeks, an immuneprofile will be performed. Two weekly injections of tumor extract will again be given in the group treated with immunotherapy.

We are not as yet in the position to present any data on the results of this study.

Immunologic Status Before and During Immunotherapy (Immuneprofile)

G. Alth,[1] H. Denck,[1] M. Fischer,[1] K. Karrer,[2] O. Kokron,[1] E. Korizek,[1] M. Micksche,[2] E. Ogris,[1] C. Reider,[2] R. Titscher,[1] and H. Wrba [2]

SUMMARY

During a prospective controlled study of patients with bronchogenic carcinoma treated with immunotherapy, an immuneprofile was performed before the start of therapy, 14 and 36 days after the start of therapy, and at the 6-week checkups. In addition to the determination of serum globulin levels, the following tests were carried out: (*a*) lymphocyte migration by tuberculin, encephalitogenic protein, and tumor extract respectively; (*b*) lymphocyte transformation by phytohemagglutinin (PHA); and (*c*) in vivo tuberculin and dinitrochlorobenzene skin reactions. An unfavorable prognostic factor is indicated by a negative tuberculin reaction associated with a failure of migration inhibition. In one patient who received treatment for 22 months, an improvement in the immune state coincided with a clinical improvement.

[Cancer Chemother Rep Part 3, vol 4:275–277, 1973]

As reported in another paper (1), the possible value of immunotherapy was suggested to us by the results of a pilot study on the treatment of inoperable bronchogenic carcinoma. In a randomized investigation using five methods of therapy, the best survival rate was in a group of patients treated with an aqueous solution of an extract of pooled bronchogenic carcinoma tissue. Of eight patients treated, two are still alive 19 and 20 months after treatment.

The extract was prepared from fresh tumor tissue obtained at operation from a minimum of six patients with bronchogenic carcinoma of different histologic types and from different blood groups. The pooled tissue had an average weight of 30 g. After removal of normal tissue the tumor material was disrupted in a saline suspension (1:2, w/v). The resulting supernatant was centrifuged at 22,000 *g* for 20 minutes and the protein content was adjusted to 1.5 mg/ml. This extract was then sealed in ampules in 1-ml amounts and injected subcutaneously (sc) twice weekly.

Immunotherapy, regardless of what is understood by the term, can only be undertaken after a series of biologic and immunologic tests. A series of tests was therefore conducted before treatment as well as 14 and 36 days after the start of treatment. During every 6–8-week checkup, all tests were repeated. A number of additional patients in the study, as well as healthy control patients and patients with other diseases, were also tested.

Together with quantitative estimation of serum globulins, the following tests for delayed hypersensitivity reactions in patients were routinely performed (fig 1):

1. Lymphocyte migration-inhibition by (*a*) tuberculin,[3] (*b*) encephalitogenic protein

[1] Krankenhaus der Stadt Wien Lainz, Vienna, Austria.
[2] Institute for Cancer Research of the University of Vienna, Austria.

[3] Tuberkulin "Sero"; Serotherapeutisches Institut Wien GmbH, Vienna, Austria.

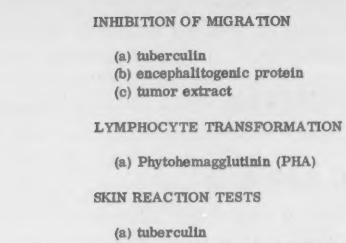

FIGURE 1.—Immuneprofile: performed before treatment, 14 and 36 days after the start of treatment, and at 6-week intervals.

(2,3),[4] and (*c*) the tumor extract used for treatment in varying concentrations.

2. Lymphocyte transformation by PHA.[5]
3. Tuberculin skin test.[6]
4. Dinitrochlorobenzene skin test.[7]

Lymphocytes for the migration test were isolated by the Ficoll-density-gradient method (4). The test was performed in Sykes-Moore Tissue Culture Chambers according to a modified technique of Falk (5), two parallel aliquots being set up with and without the test antigen. The migration area of the lymphocytes out of the capillary tubes is projected onto a paper, drawn, and cut out. It is then weighed on a high precision balance; the mean of both tests is taken as the true value. The percentage migration was then calculated as follows:

$$\frac{\text{Area of migration with antigen}}{\text{Area of migration without antigen}} \times 100.$$

The in vitro lymphocyte transformation by PHA was performed according to a modified method of Junge (6) using whole blood microcultures. DNA synthesis was studied by ^{3}H-thymidine uptake after 24 and 48 hours of culture. The dinitrochlorobenzene skin test was carried out as reported by Brown (7) using a 0.2% solution in acetone for sensitization and a 0.01% solution in acetone for challenge. The test was read 48 hours after the application of the test reagent to the skin.

A more detailed description of the techniques and results will be given elsewhere.[8] A clear correlation has not yet been found between the results of the in vivo and in vitro tests for delayed hypersensitivity as described by other investigators (8,9). Whether this correlation depends on the technique or on the lymphocyte population present in our system (with receptors of different affinity for the antigen), as reported by Nilsson (10), is under investigation. For example, in the majority of patients there is a correlation between a positive tuberculin test and the tuberculin migration test. In one of five patients, however, the results of both tests are not correlated—that is to say that with a positive tuberculin skin reaction there is no inhibition of lymphocyte migration and vice versa. In about one third of all patients, both the tuberculin migration test and the skin test are negative, indicating a particularly unfavorable prognosis in these cases.

In one patient who has been receiving continuous treatment with biweekly sc injections of tumor extract since December 18, 1970, an objective change in the tumor could be demonstrated. In February 1971, a slight regression of growth was shown by a roentgenogram, and in July and August 1971, a definite involution of the tumor in the apex of the lower lobe and in the mediastinum was seen. The patient's condition has remained stationary since then.

Immunologically, the results of immunelectrophoresis and tests for precipitating antibody with the patient's serum remain negative. Until February 1972, there was no sensitivity to tuberculin in the migration test and the tuberculin skin test remained negative. At that time, the lymphocyte transformation test was also markedly depressed.

[4] Micksche M, and Reider C. Demonstration of lymphocyte sensitization in cancer patients to a basic protein isolated from human brain, using the lymphocyte migration inhibition technique. A modified Field and Caspary Test. Unpublished data.

[5] PHA-reagent grade; Wellcome Reagents Ltd., Wellcome Research Laboratories, Beckenham, England.

[6] Tuberkulin GT; Behringwerke AG, Marburg-Lahn, Germany.

[7] 1-Chloro, 2,4-dinitrobenzol, pro analysis; Loba Chemie, Vienna, Austria.

[8] Reider C, Micksche M, Wrba H, et al. In vivo and in vitro delayed hypersensitivity reactions in patients with inoperable bronchogenic cancers (immuneprofile). In preparation.

The latest tests, done in September 1972, showed a 20% inhibition in the migration test by tuberculin and an even greater inhibition of migration by the patient's serum. A 20%–40% inhibition of migration of the patient's lymphocytes was present dependent on the addition of 0.05–0.2 ml of vaccine to the incubated lymphocytes.

The transformation test also showed an increased lymphocyte stimulation and the tuberculin skin test became positive. It is naturally of no value to speak about one case, but since this patient is the longest surviving patient having received treatment with tumor extract, and since the immuneprofile has shown definite improvement without other treatment, the case is worthy of note.

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Cell-Mediated Immunity in Lung Cancer Patients: Data, Problems, and Propositions

Lucien Israel [1]

SUMMARY

Personal data are analyzed and compared to those from other studies, not only to evaluate the depression of cell-mediated immunity in lung cancer patients, but to show (*a*) that this depression is not proportional to the spread of the disease but reflects the individual defenses; (*b*) that the state of immunity has a definite prognostic value, both in disseminated and localized cases, and can help define a poor prognosis group even in very "early" cases; and (*c*) that the immunodepressive effect of cytostatic drugs is questionable. It is proposed that these studies be extended, that patients in clinical trials be stratified according to their immunologic state, and that the immunologic changes may be correlated with the kind of therapy employed and the results registered.

[Cancer Chemother Rep Part 3, vol 4:279–281, 1973]

It is generally accepted (1–6) that cell-mediated immunity is depressed in lung cancer patients, as evaluated by skin tests to recall antigens, by challenge with dinitrochlorobenzene (DNCB), and by the in vitro response of lymphocytes to phytohemagglutinin (PHA). However, much more can be added to this crude observation and much more can be deduced from a therapeutic point of view.

We have been able to show (7, 8) that in a large series of patients there was no difference between localized and disseminated disease as far as purified protein derivative (PPD) reactivity (an antigen which still plays a very important role in the male urban population in France) is concerned. Forty-six percent of 242 patients with disseminated disease and 54% of 187 patients with localized and resectable disease in our first study had positive test results. In a more recent work devoted to squamous cell carcinoma only, we found 47% positive tests in 232 patients with disseminated disease and 51% positive tests in 323 patients with resectable disease.

These observations convince us that immunologic depression does not reflect merely and linearly the extent of the tumor and the volume of the malignant cell population. Some patients retain their immunologic responsiveness in the presence of a largely disseminated tumor and some have lost it at the time of detection and resection of a small nodule without detectable metastases. It has been shown (9) that these differences do not correlate with growth rates when evaluated in measurable tumors. The cell-mediated immunity in lung cancer patients is independent of the tumor, at least in some cases, and must be taken into account as a parameter linked with the biology of the individual patient.

Moreover, this role can be safely associated with the concept of the host's defenses, since it has been shown that cell-mediated responsiveness in lung cancer patients has a definite

[1] Centre Hospitalier Universitaire Lariboisiere, Paris, France.

prognostic value. This was the case in the study by Krant (10), in which the survival correlated with the results of the DNCB challenge at the time of diagnosis, and also in the study by Han (11), in which the frequency of occult metastases was inversely proportional to the intensity of the delayed hypersensitivity reactions. In both studies, patients with disseminated disease were studied. In a recently completed work (12), we have been able to show, using the tuberculin skin test in a large number of resectable patients (all of them having had adequate resections without any further treatment), that there was a significant correlation between the results of the skin test and the survival curves.

For 105 patients with squamous cell carcinoma and a positive tuberculin test at the time of resection, 58% were alive at 1 year, 36% at 2 years, and 21% at 4 years. The median survival time was 16+ months. For 158 patients with negative test results, the figures were respectively 41%, 25%, and 12%, with a median survival time of 8+ months. All the differences were significant at the 0.02 level. The same trends were observed in a group of 95 patients with adenocarcinoma and 33 patients with oat cell carcinoma that received resections and were followed after therapy.

It has not yet been possible to look at the distribution of the skin tests within the subgroups obtained by the TNM method of staging. Nevertheless, it already appears that the state of immunologic responsiveness (as confirmed by recent PHA tests) does have an individual prognostic value. It is thus possible to identify with more accuracy a poor prognosis group, even in cases apparently adequately resected and without nodal involvement. Obviously, there are candidates for pilot studies on adjuvant therapy using cytostatic drugs or immunostimulant drugs or both.

Finally, it has been possible in some studies to look at the changes induced in skin tests and/or tests of PHA responsiveness during therapy with so-called immunodepressing drugs (1, 13). Both studies tend to show that cytostatic treatments are immunodepressive, but there are no indications about the schedules employed.

We have treated 30 patients with a five-drug combination described elsewhere (14). Five skin tests were performed before therapy and every 2 months after therapy. After a 4-month period, there was no change in 12 patients (45%), but in 13 patients at least one test had converted to negative and in five (16.5%) at least one test had converted to positive.

This could mean that the relation between immunologic responsiveness and chemotherapy is much more complex than it has been presumed. The work of Hersh in acute leukemias (15) is of great importance in that it shows precisely that in responders, skin tests may convert to positive under chemotherapy, whereas in nonresponders, skin tests may convert to negative.

Along this line, it appears that it would probably be very useful to follow the lung cancer patients with cell-mediated responsiveness, regardless of their stage or treatment, and to attempt to correlate the following four parameters: survival, treatment regimens and schedules, side effects, and immunologic changes. Some improvement in the design of chemotherapy protocols might result from such studies.

To conclude, it seems that some agreement should be reached among institutions in various countries on the following:

(*a*) a practical set of tests should be agreed upon and employed in all cancer patients;

(*b*) an agreement should be reached on what is to be considered a positive and a negative set of tests;

(*c*) patients in clinical trials should be stratified according to the results of the pretherapeutic tests;

(*d*) tests should be performed every 2 or 3 months throughout the entire followup period and the results should be correlated with the type of therapy.

In my opinion, the analysis of the data thus obtained would rapidly lead many reluctant specialists to accept immunotherapeutic trials.

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Preliminary Results of Nonspecific Immunotherapy for Lung Cancer

Lucien Israel [1]

SUMMARY

This paper theoretically considers why nonspecific stimulation of cell-mediated immunity should be the first step in immunotherapeutic trials for solid tumors, especially for lung cancer. Also reported are the positive results on survival when *Corynebacterium parvum* is given randomly to patients with disseminated disease who are receiving chemotherapy. It is shown that in these patients *C. parvum* exerts a protective effect against the immunosuppressive effect of chemotherapy, and that its results are greater in those patients who have retained the ability to react to tuberculin. Some possible clinical trials with nonspecific immunostimulation techniques in various groups of patients are discussed in light of these results.

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The reasons for discussing only nonspecific immunotherapy for lung cancer are (*a*) manipulation of specific circulating antibodies, such as those that depress blocking antibody formation, or inoculation of unblocking antibodies is not yet operational; (*b*) instruction of lymphocytes through specific transfer factor must meet at least one requirement—that lymphocytes can be instructed, which is not the case in patients unresponsive to any kind of lymphocyte stimulation (phytohemagglutinin [PHA], re-call antigens, challenge with dinitrochlorobenzene); and (*c*) even in responsive patients, nonspecific stimulation by means of *C. parvum* has proved significantly useful (1) so that it should be used either alone or as a first step before any attempt at specific immunotherapy.

It is generally accepted, since the experimental work of Halpern (2), that BCG has a definite preventive and/or therapeutic role against experimental tumors (3–11), and the local effects of BCG injected intranodularly (12–14) are fascinating. In man, BCG has proved effective against melanoma (15–17), against advanced Hodgkin's disease (18), and in lengthening remission in acute leukemias (19). It also seems locally effective against skin metastases of breast and lung cancer (unpublished studies). It was effective in 65 advanced carcinomas (20) when used intradermally in high doses (2 mg in both arms and in both legs once a month), despite very important and long-lasting necrotic reactions.

Whether effectiveness could have been demonstrated by using BCG in scarifications, as in the studies by Bluming (21) and Mathé (22), is not known at this time. Whether BCG given intradermally or by scarification might prove effective in human carcinomas when employed for minimal residual disease also remains to be shown. Knowing that even in adequately resected lung carcinomas there are at least two poor risk subgroups, one defined by the anatomic stage and the other by the immunologic deficiency (23), it could be agreed upon that patients pertaining to both groups and receiving no other therapy should be included in clinical trials designed to evaluate the possible effect of BCG.

[1] Centre Hospitalier Universitaire Lariboisiere, Paris, France.

The experimental studies conducted to evaluate the nonspecific effect of *C. parvum* on cell-mediated immunity have been conclusive in every case (24–27). *C. parvum* can, more effectively than BCG, prevent tumor takes, enhance graft and tumor rejection, and protect against microbial infections at least as effectively as specific vaccines.

Clinically, our institution was the first (and apparently the only) institution that has tested *C. parvum* (28). To summarize the results of this first published study, it can be said that *C. parvum*, injected subcutaneously at weekly intervals at a dose of 4 mg of heat-killed cultures, proved effective in one specific situation: patients with disseminated disease treated on an intermittent schedule with five-drug combination chemotherapy. In this case the survival was significantly increased when compared to a randomized group treated with chemotherapy alone.

In addition, it could be shown that the results were significantly improved in patients with initial positive purified protein derivative (PPD) skin tests. The best group from the survival viewpoint was the one given *C. parvum* and having positive skin tests, the worst group was the one not given *C. parvum* and having negative skin tests, and in between was the group having positive skin tests and not given *C. parvum*. This group did slightly, but not significantly, better than the group given *C. parvum* but having negative tests.

Another point could be demonstrated: the advantage was not due to an increase in response rates but to a prolongation of the duration of response or to a prologation of stabilization periods.

It follows from the above results that (*a*) immunostimulation can be effective in patients with advanced and disseminated disease; (*b*) chemotherapy (at least on an intermittent schedule) does not mask the effectiveness of immunostimulation; and (*c*) *C. parvum* increases the survival both in the patients who have retained and those who have not retained the ability to show delayed hypersensitivity reactions.

Another study [2] has shown that *C. parvum* is a good protection against the possible immunodepressive effects of chemotherapy. The results among three groups of patients tested at the beginning of therapy and at 4 months after therapy by means of PPD, mumps antigen, candidin, and a microbial antigen (C.C.B. Pasteur), and challenged with dinitrochlorobenzene are shown in table 1. These results take into account the conversion to positive or negative of at least one test.

Finally, two studies are still under way, both devoted to assess, by comparison with controls, the effectiveness of *C. parvum* in delaying recurrence after removal of the primary tumor in melanoma and in squamous cell bronchogenic lung carcinoma. In both studies, the figures achieved at the present time enable us to predict that the results will be conclusive. Patients in these series have been or are being treated for 1 year with weekly injections of *C. parvum*.

All the facts mentioned above are not definitely conclusive. If they were, there would be no need for further studies and clinical trials. On the basis of what is now known it is possible to agree that (*a*) nonspecific immunostimulation, be it by means of BCG or

[2] Israel L. Clinical results with *Corynebacteria*. Presented at the Symposium on Cellular Immunity and Immunotherapy in Cancer Patients, Paris, June 1972. To be published.

TABLE 1.—Immunodepressive effects in patients tested (by means of PPD, mumps antigen, candidin, C.C.B. Pasteur, and DNCB) before and 4 months after immunotherapy or chemotherapy or both

Treatment	No change	Positivation	Negativation
Chemotherapy alone	40%	15%	45%
C. parvum alone	40%	40%	20%
Chemotherapy plus *C. parvum*	33%	59%	8%

C. parvum, is feasible and safe in lung cancer patients; (*b*) it has sufficient promise to deserve well-designed trials, in view of the fact that results obtained by conventional means in lung cancer have not improved for years (29); and (*c*) for cooperative trials some specific groups of patients can be recommended.

From what has been shown above I think that the following groups of patients should be submitted to trials exploring the possibilities of nonspecific immunostimulation:

1. Poor-risk surgical patients, that is, patients who have had resections but who are in the N_1 or N_2 category and who, moreover, have negative skin tests and/or are unresponsive to PHA tests. These patients do not generally receive treatment after surgery has been completed unless recurrence or metastases appear.
2. Patients submitted to radiation therapy for localized unresectable disease and not treated afterwards by chemotherapy for various reasons (including reluctance of their physician or radiotherapist).
3. Patients with disseminated disease treated by chemotherapy. Once a given regimen has been agreed upon within a group of therapists, a randomization could be done to see if there is some advantage in adding nonspecific immunostimulation to the cytostatic treatment.

Of course, it remains to be determined if BCG or *C. parvum* or both could be used as a means of nonspecific immunostimulation. Here again, these questions must be answered by means of clinical trials. We have reached the time when clinical trials on immunotherapy in lung carcinomas are necessary.

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"Immune" RNA—A New Model for the Immunotherapy of Cancer [1]

Yosef H. Pilch [2]

SUMMARY

Normal, nonimmune lymphoid cells are made specifically immunoreactive by incubation with preparations rich in RNA extracted from the lymphoid organs of immunized animals. Such RNA-incubated lymphoid cells are then capable of mediating immunity to specific tumor isografts in vivo and immune cytolysis of tumor target cells in vitro. These preparations of "immune" RNA have also been effective in transferring tumor-specific immunity directly when administered systemically in media containing a ribonuclease inhibitor to previously untreated hosts. "Immune" RNA may provide a new modality for immunotherapy for cancer in man.
[Cancer Chemother Rep Part 3, vol 4:287–292, 1973]

In recent years, a number of laboratories have studied the apparent conversion of normal, nonimmune lymphoid cells to specifically immunoreactive cells after incubation in vitro with RNA-rich extracts prepared from lymphoid tissues or macrophages following exposure to specific antigens either in vivo or in vitro (1–6).

The transfer of immunity to cellular antigens has also been accomplished with such preparations of "immune" RNA. In 1964 Mannick and Egdahl (7) reported the transfer of transplantation immunity by incubation of autologous spleen cells with RNA extracted from regional lymph node cells of specifically immunized rabbits. Reinfusion of these RNA-incubated spleen cells caused accelerated rejection of skin allografts taken from the same animal used to immunize the RNA donor. These findings have since been confirmed by Sabbadini and Sehon (8) and in our own laboratory (9). Moreover, Wilson and Wecker (10) and Bondevik and Mannick (11) have demonstrated that nonimmune lymphoid cells incubated with RNA extracted from the lymphoid organs of animals immunized to histocompatibility antigens cause specific immune cytolysis of target cells in vitro. Since immunity to transplantation antigens could be mediated by "immune" RNA, it seemed likely that immunity to tumor-specific transplantation antigens (TSTA) could also be transferred with RNA.

Alexander et al (12,13) reported growth retardation and occasional temporary regression of 3,4-benzpyrene-induced sarcomas in rats treated by footpad injections of RNA extracted from the lymph cells of sheep immunized with the particular rat tumor being treated. Rigby (14) prolonged the survival of mice bearing Ehrlich ascites tumors by administering syngeneic spleen cells previously incubated with RNA from the spleens of mice immunized with this tumor. Londner et al (15) demonstrated a slowing of the growth of transplants of a spontaneously arising sarcoma in rats treated by the intraperitoneal (ip) injection of RNA extracted from the spleens of rats immunized with the tumor being treated. Recently, Kennedy et al (16) reported the protection of C3H mice against transplants of a benzo-[a]pyrene-induced sarcoma by footpad injections of RNA extracted from the lymph nodes

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[2] Division of Oncology, Department of Surgery, University of California, Los Angeles, and Veterans Administration Hospital, Sepulveda, Calif.

and spleens of C57BL mice immunized with this tumor.

MEDIATION OF IMMUNITY TO MURINE TUMOR ISOGRAFTS BY XENOGENEIC "IMMUNE" RNA

Our laboratory adapted the model of Mannick and Egdahl to study the mediation of immunity to tumor-specific antigens by RNA preparations extracted from the lymphoid organs of rodents immunized to tumors. We demonstrated that immunity to murine tumor isografts could be transferred to previously untreated mice by the ip administration of syngeneic spleen cells pre-incubated with RNA extracted from the lymph nodes and spleens of guinea pigs immunized with the particular mouse tumor being treated (17–19). The effects observed in this system were abolished by treatment of the active RNA extracts with ribonuclease but treatment with deoxyribonuclease or pronase did not affect activity. In this system, the guinea pigs were immunized to murine transplantation antigens as well as to tumor-specific transplantation antigens. However, RNA extracted from the lymphoid organs of guinea pigs immunized with normal murine tissues failed to mediate an antitumor response; this indicated that the response was tumor specific (18,19). The immunity was also shown to be specific for the particular tumor used to immunize the guinea pigs from which the "immune" RNA was prepared (19). These two findings provided *indirect* evidence of the specificity of these reactions for the TSTA of the murine tumor.

MEDIATION OF IMMUNITY TO TUMOR ISOGRAFTS BY SYNGENEIC "IMMUNE" RNA

In order to obtain *direct* evidence that "immune" RNA could mediate immune responses to TSTA, it was necessary to use a system in which the tumor cells, the lymphoid tissues from which RNA was extracted, the spleen cells incubated with the RNA, and the recipient host were all from a single, inbred strain of animal. This would eliminate the possibility that the inhibition of tumor isograft development observed might be due, in part, to immune responses directed against transplantation antigens. Recent reports from our laboratory (17,20) have described the immune cytolysis of strain 2 guinea pig tumor cells in vitro by syngeneic spleen cells pre-incubated with RNA extracted from the spleens of strain 2 guinea pigs immunized by amputation of growing transplants of the same tumor. This study demonstrated in vitro for the first time the mediation of an immune response to tumor-specific antigens by syngeneic "immune" RNA. In all earlier studies of the transfer of transplantation or tumor immunity with RNA, whether in vitro or in vivo, allogeneic or xenogeneic lymphoid cells or tissues were utilized as sources of "immune" RNA. It remained to demonstrate that syngeneic "immune" RNA extracted from the lymphoid tissues of inbred animals immunized only to the TSTA of an experimental tumor could mediate an antitumor immune response in vivo. Therefore, experiments were designed to study the transfer of immunity to TSTA in vivo in an experimental rodent system in which the tumor cells, RNA donor, spleen cells, and recipient animals would all be from a single, inbred strain. The results of these experiments have been reported in detail elsewhere (21).

A benzo[*a*]pyrene-induced sarcoma designated BP–1R (induced and carried in inbred, female Fisher 344N rats) was used in early transplant generations. This sarcoma had previously been shown to possess tumor-specific transplantation antigens (22). Fisher rats were immunized by the excision of growing tumor transplants, and then boosted at weekly intervals with viable BP–1R cells. All of these inocula of viable tumor cells were rejected. One week after the last injection of tumor cells, the rats were killed, their spleens were excised, and RNA was extracted. Suspensions of normal Fisher 344 spleen cells were incubated in this RNA, washed, and then injected daily intravenously (iv) into normal Fisher rats for 3 days. At the time of the first injection of spleen cells, each rat received a challenge inoculum of viable BP–1R cells. A control group of rats was treated with Fisher spleen cells incubated with RNA extracted from the spleens of unimmunized Fisher rats. Another control group of animals received no spleen

cells at all. All animals were observed for tumor development, and all tumors which developed were measured at biweekly intervals and tumor volumes were calculated.

The rats that were challenged with BP–1R tumor cells and treated with syngeneic spleen cells pre-incubated with RNA extracted from the spleens of rats immunized with the BP–1R sarcoma evidenced a significantly lower incidence of tumor isograft development than did rats in any control group. The injection of syngeneic spleen cells alone, without incubation with RNA of any type, had no demonstrable antitumor effect. Furthermore, one or more species of RNA appeared to be the active moiety in our "immune" RNA extracts since rats receiving spleen cells incubated with the same active "BP–1R immune" RNA preparation, but treated with ribonuclease prior to incubation with the spleen cells, manifested a tumor incidence similar to that of the challenged control animals.

TRANSFER OF IMMUNITY TO TUMOR ISOGRAFTS BY DIRECT SYSTEMIC ADMINISTRATION OF "IMMUNE" RNA

It then seemed apparent that a simpler and more direct method of utilizing "immune" RNA in mediating antitumor immune responses would be the direct systemic administration of "immune" RNA itself rather than lymphoid cells preincubated with RNA.

Ribonuclease is known to inactivate preparations of "immune" RNA (17,19,20), and plasma and interstitial fluid contain significant levels of ribonucleases. These facts led to the initial assumption that the direct systemic administration of "immune" RNA without lymphoid cells would be ineffective because of the enzymatic degradation and inactivation of "immune" RNA by interstitial fluid and plasma ribonucleases. We attempted to eliminate this problem by administering our "immune" RNA in a solution containing a potent ribonuclease inhibitor. Many polyanions are excellent inhibitors of ribonuclease (23,24); the ribonuclease inhibitor that we selected was the polyanion, sodium dextran sulfate.

Therefore, experiments were undertaken to study (*a*) the direct systemic administration of "immune" RNA within two tumor-host systems in inbred rodents, and (*b*) the efficacy of administering "immune" RNA in solutions containing a ribonuclease inhibitor. These experiments have been described in detail in a previous report (25). In both tumor-host systems, the transfer of immunity to tumor isografts had been accomplished earlier by the administration of syngeneic spleen cells preincubated in vitro with RNA extracted from the lymphoid organs of animals immunized with the same tumor (17,19).

Again, the BP–1R rat sarcoma was used. Hartley guinea pigs were immunized with BP–1R cells and RNA was extracted from their lymph nodes and spleens. A control RNA preparation was also extracted from the nodes and spleens of unimmunized pigs. Sodium dextran sulfate, molecular weight 77,500, was added to each RNA preparation to a final concentration of 10 mg/ml. The RNA-dextran sulfate mixtures were then administered (as 0.25-ml doses injected into each footpad) to groups of normal Fisher rats every other day for 10 days. On the first day, each rat also received a subcutaneous (sc) challenge inoculum of viable BP–1R cells. Other control rats received footpad injections of dextran sulfate only or no treatment at all. Recipients of RNA from guinea pigs immunized with BP–1R exhibited significant resistance to the growth of isografts of BP–1R compared with untreated rats, rats that received dextran sulfate alone, or rats that received "nonspecific" RNA.

Similar experiments were performed in a syngeneic murine tumor-host system. Two benzo[*a*]pyrene-induced fibrosarcomas (designated BP–1 and BP–4) induced and carried in C3Hf/HeN female mice were used. Both tumors contained distinct and non-cross-reacting tumor-specific transplantation antigens. Hartley guinea pigs were immunized as described earlier with either BP–1 or BP–4 sarcoma cells, and RNA was extracted from their lymphoid organs 9–11 days after immunization. Control RNA was extracted from the lymphoid organs of guinea pigs immunized with C3H/HeN normal tissues (lung, liver, kidney, and spleen) instead of tumor cells. RNA preparations used in these experiments were: (*a*)

RNA from the lymphoid organs of guinea pigs immunized with the BP–4 sarcoma (BP–4 RNA); (*b*) RNA from guinea pigs immunized with the BP–1 sarcomas (BP–1 RNA); (*c*) RNA from guinea pigs immunized with normal C3H tissues (C3H RNA); and (*d*) BP–4 RNA treated with ribonuclease (BP–1 RNA-ribonuclease). Sodium dextran sulfate, molecular weight 500,000, was then added to the RNA preparations to a final concentration of 3 mg/ml. One RNA preparation, BP–4, was administered without dextran sulfate. The RNA-dextran sulfate mixtures were then administered (as 0.25-ml doses injected sc into each limb) to groups of normal C3H/HeN mice every other day for 6 days. On the first day, all mice received an sc challenge inoculum of either BP–4 or BP–1 tumor cells.

Mice inoculated with BP–4 or BP–1 tumor cells and then treated with sc injections of tumor-specific "immune" RNA demonstrated significant inhibition of tumor development when compared with mice that received tumor cells alone. Treatment of the active RNA preparations with ribonuclease abolished this response. Specificity for the immunizing tumor was demonstrated by failure of the BP–1 RNA preparation to inhibit isografts of BP–1. Tumor specificity was also shown by the fact that normal tissue RNA (C3H RNA) was ineffective. The failure of BP–4 RNA without dextran sulfate to inhibit the development of isografts of BP–4 indicated the importance of combining "immune" RNA with a ribonuclease inhibitor, such as dextran sulfate. Dextran sulfate presumably acts by preventing degradation of the "immune" RNA by endogenous ribonucleases. Further investigations are required to establish (*a*) the optimal dosage and injection schedule of "immune" RNA, (*b*) the most efficacious type and concentration of ribonuclease inhibitor, and (*c*) the optimal concentration of "immune" RNA.

DISCUSSION

We think that the experiments described in this paper constitute a new animal model for the immunotherapy for cancer in man. In this model, xenogeneic "immune" RNA extracted from the lymphoid organs of animals immunized with human tumor tissue could be utilized. This would eliminate the necessity of obtaining allogeneic RNA from human subjects. Xenogeneic RNA has been shown to mediate tumor-specific immune responses that are specific for the immunizing tumor and do not appear to be directed against normal transplantation antigens (19). Moreover, animals treated with xenogeneic "immune" RNA have evidenced no significant toxic reactions. "Immune" RNA could be extracted from the lymphoid organs of animals immunized by allogeneic human tumor cell lines carried in tissue culture for this purpose. Alternatively, xenogeneic, allogeneic, or perhaps autologous, normal lymphoid cells could be sensitized in vitro to human tumor cells, and then extracted and used as a source of "immune" RNA. This "immune" RNA might be administered to patients by multiple intradermal or sc injections in a solution containing a ribonuclease inhibitor such as dextran sulfate. Alternatively, autologous lymphocytes could be removed from patients by the National Cancer Institute blood cell separator. These autologous lymphocytes could then be incubated in vitro with xenogeneic "immune" RNA, washed once or twice, and then reinfused.

Immunotherapy with "immune" RNA might offer several advantages over existing methods of immunotherapy. It would obviate the administration of "immune" antisera or plasma. Treatment with such antisera might result in enhanced tumor growth because of the presence of enhancing or "blocking" antibodies. It would also obviate the administration of allogeneic leukocytes, which can result in sensitization to leukocyte isoantigens. Repeated transfusion of allogeneic leukocytes might then result in significant toxicity. Moreover, the immune elimination of allogeneic leukocytes might make subsequent transfusions of such cells ineffective for immunotherapy. If the immune system of the patient with cancer is defective, the possibility of the induction of a graft-versus-host reaction also exists. "Immune" RNA itself may not be a strong antigen and, therefore, injections of RNA, even xenogeneic RNA, would not be expected to sensitize the recipient, to cause secondary syndromes, or to result in immune elimination of the RNA.

Although application of our findings to the immunotherapy of cancer in man has yet to be accomplished, we think that "immune" RNA offers many exciting possibilities as a new modality for the immunotherapy of cancer in man.

The possible mechanisms by which such preparations of "immune" RNA may act to mediate tumor-specific transplantation immunity include: (*a*) the simple passive transfer of tumor antigen as contaminants in the RNA preparations, (*b*) the formation of highly immunoreactive RNA-antigen complexes or "super antigens," and (*c*) the transfer of a type of true informational RNA which can be incorporated by lymphoid cells and code for a specific immune response. The first possibility seems quite unlikely. There is evidence that suggests that tumor antigens, like rodent transplantation antigens, have the chemical properties of proteins. Most protein antigens would be denatured and inactivated by phenol treatment during RNA extraction. Also, Ramming and Pilch have demonstrated that our active RNA preparations are not inactivated by treatment with pronase (17,19). We have no data to suggest which of the other two mechanisms is operative in our system. There is evidence to support both theories. Indeed, Fishman and Adler have shown that both mechanisms may be operative simultaneously (26). They demonstrated that two classes of immunologically active RNA could be extracted from rat peritoneal exudate cells exposed to T2 phage antigen in vitro. One type of "immune" RNA contained no detectable antigen and induced IgM antibody production, whereas the other was associated with detectable amounts of antigen and induced IgG antibody formation.

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Adjuvant Immunotherapy for Bronchogenic Carcinoma: Preliminary Results

Hiroshi Takita and Antonio Brugarolas [1]

SUMMARY

Five patients with locally advanced bronchogenic carcinoma were treated with autologous tumor vaccine after incomplete surgical resection. An improvement in the survival of the treated group compared with that of the control group was noted. Three of the five patients treated with tumor vaccine are alive (mean survival time, 18.8 months), whereas all six patients in the control group (no adjuvant immunotherapy) have died (mean survival time, 7.5 months).

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Although immunotherapy for cancer has been discussed often lately, the basis for immunologic intervention remains mostly empirical because the mechanism of action is poorly understood (1–4). Bronchogenic carcinoma appears to be suitable for the investigation of the effect of immunotherapy because of the consistent association between immunologic deficit and progression of the disease (5). Moreover, there has been no effective therapy other than surgical resection.

We treated patients with locally advanced bronchogenic carcinoma with tumor vaccine after incomplete resection and compared the results obtained in these patients with the results obtained in a group of patients with a comparable extent of disease who did not receive adjuvant immunotherapy. The results of this study are presented in this paper.

MATERIALS AND METHODS

Patients

Eleven patients underwent incomplete resection of locally advanced bronchogenic carcinoma. After surgical treatment, these patients were randomized into two groups. Patients in Group 1 received no immunotherapy; patients in Group 2 received adjuvant immunotherapy. Postoperative radiation therapy was given to patients of both groups when the tumor involved the chest wall or when the line of bronchial resection contained tumor.

Group 1: Six patients served as controls. Two of these patients received postoperative radiation therapy. The other four patients received no treatment until manifestation of recurrence or metastasis.

Group 2: Five patients received adjuvant immunotherapy. Two of these patients also received postoperative radiation therapy.

Preparation of Tumor Vaccine

Autologous tumor cells were used. Two patients received tumor vaccine prepared according to the method described by Czajkowski et al (6). The method consisted of chemical coupling of the fresh autologous tumor cells to a highly antigenic foreign protein with bis-diazobenzidine and reinjection of this complex together with complete Freund's adjuvant back into the same patient. The other three patients

[1] Department of Thoracic Surgery, Roswell Park Memorial Institute, New York State Department of Health, Buffalo.

received tumor vaccine consisting of autologous tumor cells coated with concanavalin A. This method was selected because of its superiority to Czajkowski's method in animal experimental models (7). Freshly obtained tumor cell suspension was incubated at 37 C for 30 minutes with concanavalin A (10–20 $\mu g/10^6$ viable tumor cells). The tumor cells were subsequently washed three times, and a final suspension containing 10^6 tumor cells/ml was prepared. One ml of concanavalin-A-coated tumor cells was injected together with 0.5 ml of Freund's adjuvant.

Administration of Tumor Vaccine

Part of the tumor vaccine was injected intradermally and part was injected subcutaneously into the thigh or arm; each injection was given at a different site. The first injection was given on the day the tumor was harvested. Subsequent injections were given at 2-week intervals for 2 months.

Followup

Skin tests to determine reactivity to common antigens (candida, mumps, purified protein derivative [PPD], and streptodornase-streptokinase) were performed on all patients prior to therapy and every 2–3 months afterwards. Laboratory tests included blood cell counts, immunoglobin determinations, and in vitro lymphocyte stimulation tests.

RESULTS

The course of disease and the current status of the patients are described in table 1. All six patients in the control group died, whereas three of the five patients treated with adjuvant immunotherapy are alive. All six patients in the control group had recurrence of disease, but only three of the five patients in the treated group had recurrence of disease. The mean survival time of the control group is 7.5 months and that of the treated group is 18.8 months.

TABLE 1.—Adjuvant immunotherapy for bronchogenic carcinoma

Treatment group	Patient No.	Disease		Therapy	Recurrence (mos after operation)	Therapy for recurrent disease	Status (mos after operation)*
		Pathology	Extent				
Control (Group 1)	1	Glandular	Mediastinal nodes	Incomplete surgical resection	10	Chemotherapy, radiation therapy	Dead (19)
	2	Squamous cell	Chest wall, hilar nodes	Incomplete surgical resection, radiation therapy	4	Chemotherapy, radiation therapy	Dead (10)
	3	Glandular	Mediastinal nodes	Incomplete surgical resection	2	Chemotherapy	Dead (6)
	4	Squamous cell	Mediastinal nodes	Incomplete surgical resection	2	Chemotherapy	Dead (4)
	5	Glandular	Mediastinal nodes	Incomplete surgical resection	2	—	Dead (3)
	6	Squamous cell	Chest wall, hilar nodes	Incomplete surgical resection, radiation therapy	2	Chemotherapy	Dead (3)

TABLE 1.—Adjuvant immunotherapy for bronchogenic carcinoma—Continued

Treatment group	Patient No.	Disease		Therapy	Recurrence (mos after operation)	Therapy for recurrent disease	Status (mos after operation)*
		Pathology	Extent				
Adjuvant immunotherapy (Group 2)	7	Glandular	Mediastinal nodes	Incomplete surgical resection, tumor vaccine	18	Radiation therapy	Dead (25)
	8	Squamous cell	Mediastinal nodes	Incomplete surgical resection, tumor vaccine	—	—	Alive, NED (31)
	9	Glandular	Chest wall, bronchial stump†	Incomplete surgical resection, tumor vaccine, radiation therapy	—	—	Alive, NED (15)
	10	Squamous cell	Mediastinal nodes, bronchial stump†	Incomplete surgical resection, tumor vaccine, radiation therapy	8	—	Dead (8)
	11	Glandular	Bilateral mediastinal nodes	Incomplete surgical resection, tumor vaccine	5	Chemotherapy	Alive with tumor (15)

*NED = no evidence of disease.
†Bronchial stump: line of resection positive for tumor.

Side Effects of Tumor Vaccination

Local Reaction

Erythema and edema were noted at the injection site 1 day after the first vaccination. These changes gradually subsided over a period of 4–5 days. A small induration often remained after the initial reaction disappeared. Local reaction after the second and subsequent vaccinations was more intense and lasted 4–5 days. At times, moderate erythema and edema were noted simultaneously at the previous vaccination sites. In one half of the patients, the vaccination site eventually became ulcerated and slowly healed in 1–2 months.

Histologic study of the vaccination site 4 days after the first vaccination revealed the presence of the inoculated tumor cells surrounded by edema and a small amount of white blood cell infiltration (fig 1). Biopsy of the second vaccination site revealed a marked degree of lymphocyte infiltration (fig 2).

Systemic Reaction

No systemic reactions were observed after tumor vaccination.

DISCUSSION

Although there have been reports of successful tumor immunotherapy in patients with disseminated carcinoma (6,8), the most favorable results reported have occurred in patients whose tumors had been reduced to a minimum

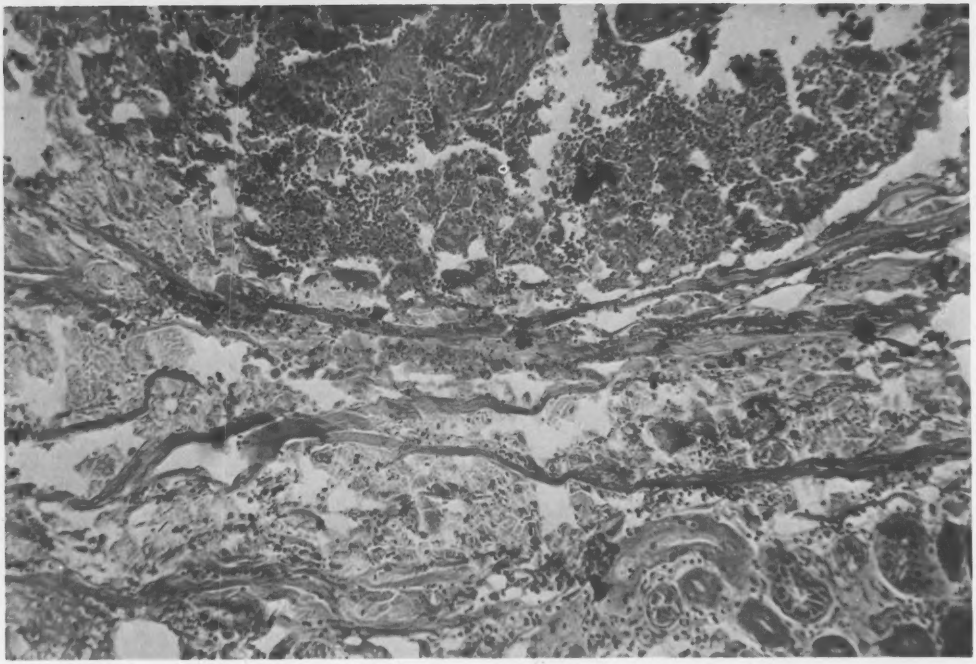

FIGURE 1.—Histologic appearance of the first vaccination site (× 180).

by surgical resection (9), or by chemotherapy (10) prior to immunotherapy. These encouraging reports seem to support the hypothesis of Mathé (10) that immunotherapy may be able to control the last tumor cell after effective chemotherapy.

In patients with bronchogenic carcinoma, palliative surgical excision is not practiced conventionally because there is no known effective adjuvant radiotherapy or chemotherapy (11,12). However, our present results, although preliminary and based on a small series of patients, suggest that immunotherapy used as an adjuvant to radical surgical resection might be of benefit in those patients who have tumors that are advanced locally but confined to the thorax (mediastinal node metastasis, or chest wall or mediastinal invasion). These patients have been known to maintain good cellular immunity (5); thus, they may be able to react favorably to the stimulation of immunotherapy.

There are several objections to the use of autologous tumor cells or tumor cell extract for immunotherapy. One objection is based on the limited availability of autologous tumor cells and the difficulty in preserving live cells. A second and more important objection is that the tumor cells might induce the formation of enhancing antibodies (13,14). Since the presence of tumor-specific antigen in lung cancer has not been reported and since it is not possible at the present time to detect such antibodies, the danger of tumor enhancement remains empirical. We have not observed enhancement of growth as a result of tumor vaccination.

For these reasons, immunotherapy with non-

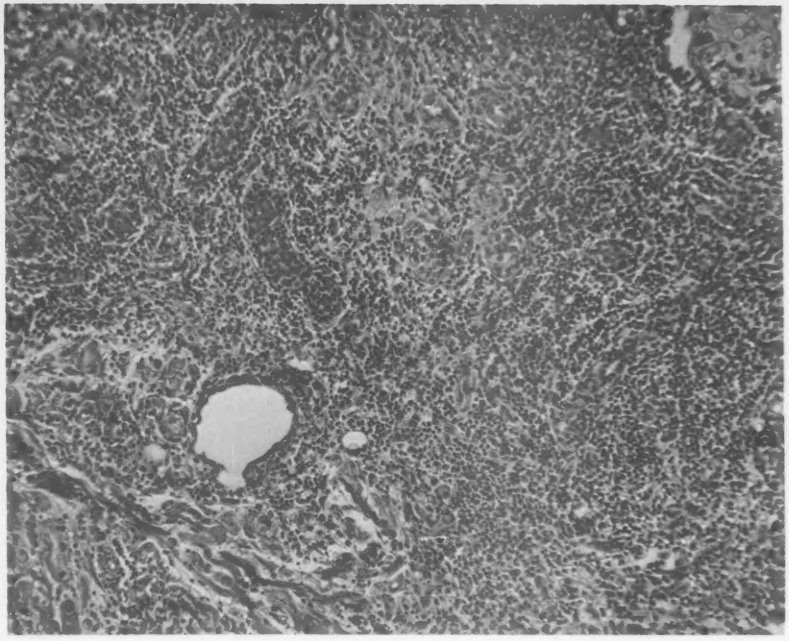

FIGURE 2.—Histologic appearance of the second vaccination site (× 180).

specific immunostimulants (bacillus Calmette Guérin [BCG] and *Corynebacterium parvum*) has been advocated. The mechanisms involved are not clear, but Israël et al (15) and Hadžiev et al (16) have reported encouraging results.

There are, however, objections to the use of nonspecific immunotherapy alone. First, nonspecific immune stimulation would be effective only if the host recognizes the tumor cell as antigen. Another possible argument against the use of BCG alone in immunotherapy for lung cancer comes from the fact that lung cancer frequently arises in patients who have or have had tuberculosis (17). It may also be possible that the benefit of nonspecific stimulation in the reported trials referred to in this paper was due not to antitumor effect but to an improvement in the general condition of the patients since a considerable proportion of patients with bronchogenic carcinoma die from pneumonia or intercurrent infectious diseases and improvement in survival in the reported series could have been due to increased resistance to infection.

This report in itself is not evidence supporting a method of immunotherapy, but a preliminary observation on the possible adjuvant effect of immunotherapy following incomplete surgical resection of bronchogenic carcinoma.

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PANEL REPORT

Morphologic Classification of Bronchogenic Carcinoma

Mary J. Matthews [1]

The Pathology Panel of the International Workshop for Therapy of Lung Cancer was charged with agreeing upon a classification of lung tumor, based on and compatible with the classification proposed through the World Health Organization (WHO) in 1967 by Kreyberg et al(1). Slight modifications of this system were considered advisable to permit maximum evaluation of cell type and to minimize inconsistencies known to occur in surgical and biopsy materials. The amended form, with definitions of cell types (Appendix A), was accepted by the Panel and recommended for use by members of the Workshop. Panel members included the pathology panel of the Veterans' Administration Lung Cancer Study Group (Drs. Oscar Auerbach,[2] Bruno Gerstl,[2] and Raymond Yesner [chairman]); the pathology committee of the Working Party for Therapy of Lung Cancer (Drs. John Lukeman, Mary Matthews [chairman], James Parker,[2] John Pickren, C. J. Uys, and Lewis Woolner [2]); and national and international guests (Drs. Johannes Clemmesen, Suryabala Kanhouwa, Ralph Powell, and Franco Rilke).

Table 1 outlines the classification of lung tumors as recommended by the WHO and the modifications proposed by the Pathology Panel.

Since patients will be placed in most lung

[1] National Cancer Institute-Veterans' Administration Medical Oncology Service, VA Hospital, Washington, DC, and the NCI, Bethesda, Md.

[2] Unable to attend the Workshop.

TABLE 1.—Comparison of the World Health Organization classification and modifications suggested by the Pathology Panel

World Health Organization classification	Proposed modifications
I. Epidermoid carcinoma	10. Epidermoid carcinoma 11. Well-differentiated 12. Moderately differentiated 13. Poorly differentiated
II. Small cell anaplastic carcinoma 1. Fusiform 2. Polygonal 3. Lymphocyte-like 4. Others	20. Small cell anaplastic carcinoma 21. Lymphocyte-like (oat cell) 22. Intermediate cell (fusiform, polygonal, others)
III. Adenocarcinoma 1. Bronchogenic *a.* Acinar *b.* Papillary 2. Bronchioloalveolar	30. Adenocarcinoma 31. Well-differentiated 32. Moderately differentiated 33. Poorly differentiated 34. Bronchioloalveolar/papillary
IV. Large cell carcinoma 1. Solid tumors with mucin 2. Solid tumors without mucin 3. Giant cell 4. Clear cell	40. Large cell carcinoma (40/30) with mucin production (40/10) with stratification 41. Giant cell 42. Clear cell

10. Epidermoid carcinoma

    11.0 Well-differentiated: Tumors are characterized by polygonal or prickle-type cells, stratification, intercellular bridge formation; individual cell keratinization and/or tendency to form epithelial pearls; nuclei may be uniform, pleomorphic, or giant.

    12.0 Moderately differentiated: Tumors are characterized by polygonal or prickle-type cells, stratification, intercellular bridge formation; some attempt at keratinization; nuclei are variable, pleomorphic, or giant.

    13.0 Poorly differentiated: Tumors are composed predominantly of anaplastic cells, with little but distinct evidence of intercellular bridge formation and/or individual cell keratinization. Without these latter markers a tumor will not be placed in this category.

20. Undifferentiated/anaplastic small cell carcinoma

    21.0 Small cell (oat-/lymphocyte-like): Tumors are characterized by clusters, nests, or sheets of cells with small dark oval or round nuclei, with delicate chromatin and absence of prominent nucleoli; nuclei are essentially naked and devoid of cytoplasm; cells are supported by a vascular fibrous stroma; crush phenomenon is usually present.

    22.0 Intermediate (polygonal/fusiform) cell: Tumors are composed of clusters, nests, or sheets of small cells with slightly larger, more vesicular, fusiform, oval, or polygonal nuclei than cells described in 21.0. Cytoplasm is scanty or indistinct; cells are supported by a fibrous stroma. Crush phenomenon is usually present. Tubular or rosette patterns may be present.

30. Adenocarcinoma

    31.0 Well-differentiated: Tumors are composed of cuboidal to columnar epithelial cells with fairly uniform round nuclei, adequate to abundant pink or vacuolated cytoplasm, arranged in distinct acinar or glandular patterns, supported by a fibrous stroma. May show papillary intraluminal growth or contain mucicarmine-positive vacuoles or secretions.

    32.0 Moderately differentiated: Tumors are composed of nests, cords, or isolated cells, occasionally arranged in acinar or glandular pattern, with pleomorphic nuclei, prominent nucleoli, and moderate amounts of cytoplasm; cells are supported by a fibrous or desmoplastic stroma; may contain mucicarmine-positive vacuoles or secretions.

    33.0 Poorly differentiated: Tumors are composed predominantly of anaplastic cells of variable size and shape; minimal but distinct evidence of acinar formation. Mucicarmine vacuoles may be present. Without distinct acinar formation, tumors will not be placed in this category.

    34.0 Bronchioloalveolar/papillary: Tumors are composed of tall columnar epithelial cells, with uniform to pleomorphic nuclei, abundant vacuolated cytoplasm, with a predominant tendency to use alveolar walls as a framework or stroma; may be papillary, mucous producing, and associated with some degree of desmoplasia. Tumors with dominant papillary pattern will be placed in this category.

40. Anaplastic/undifferentiated large cell carcinoma:

    40.0 Tumors show no evidence of maturation or differentiation: Cells are arranged in clusters, nests, strands, or in isolated-cell pattern; have pleomorphic enlarged irregular vesicular or hyperchromatic nuclei and prominent nucleoli. Cytoplasm is abundant, clear, vacuolated, or amphophilic; cells may contain

APPENDIX A—Amended classification of lung tumors suggested by Pathology Panel—Continued

cytoplasmic hyalin droplets or intranuclear inclusions; multinucleated giant cells and mucicarmine-positive vacuoles may be present. Tumors that tend to stratify but show no evidence of keratin or intercellular bridge formation will be classified as large cell (anaplastic) carcinoma (40/10). Tumors that show evidence of mucin formation but do not form glands will be classified as large cell (anaplastic) carcinomas (40/30).

41.0 Giant cell carcinoma: Tumor similar to that described above. The majority of cells have pleomorphic nuclei and abundant cytoplasm; 30%–50% of the cells are multinucleated or have giant nuclei.

42.0 Clear cell carcinoma: Tumors are predominantly composed of nests or clusters of large cells with almost totally clear cytoplasm, without evidence of maturation to epidermoid or glandular pattern.

cancer protocols according to major cell types, inclusion of stages of differentiation in the epidermoid and adenocarcinoma categories was considered desirable for academic purposes. Such distinctions may provide the clinician, statistician, and pathologist with a mechanism for determining if there are, in fact, significant variances in behavioral and therapeutic response of these subtypes. It is quite possible that overlapping of moderately and well-differentiated patterns, or moderately and poorly differentiated patterns in many tumors, will blur or erase any measurable variation.

In an attempt to improve consistency and reliability in diagnoses, only those anaplastic tumors that show some evidence of intercellular bridge formation and/or minimal keratinization will be classified as poorly differentiated epidermoid malignancies. Similarly, only those anaplastic tumors which show some distinct evidence of acinar formation will be classified as poorly differentiated adenocarcinomas. So-called anaplastic squamoid tumors that stratify but contain no other markers will be placed in the large cell carcinoma category. To retrieve these tumors for statistical, reliability, and comparability purposes, they will be designated (40/10). Anaplastic tumors which show some evidence of mucin production but no acinar formation will also be placed in the large cell category and designated (40/30). Such a concept is basically in keeping with the WHO classification (IV, 1 and 2). It is recognized that many of these tumors can and will be more precisely diagnosed at autopsy. Since the majority of these tumors prove to be poorly differentiated adenocarcinomas, it would seem desirable that large cell carcinomas and adenocarcinomas share the same therapeutic regimen when protocols are designed.

In the small cell carcinoma category, the lymphocyte-like variant presents minimal diagnostic problems. Other subtypes in this category (including the fusiform cells, polygonal cells, or those which tend to form rosettes, tubules, or syncytial giant cells) are, in fact, intermediate in size and occasionally difficult to recognize in metastatic sites. It did not seem feasible to subdivide this group further.

Bronchioloalveolar malignancies present a special problem. The diffuse lobar variety is rarely seen except at autopsy. The multicentric type may be seen at surgery but its primary nature often remains in doubt until autopsy. The subpleural papillary adenocarcinomas, frequently associated with scars, may be considered bronchiolar in origin; however, they behave quite differently from the classical bronchioloalveolar tumors, are often clinically occult, and may present with distant metastases. It is felt that it is almost impossible to distinguish such papillary tumors from bronchioloalveolar tumors, particularly in metastatic foci, and that the two should be combined in the proposed modified classification.

The proposed classification will be evaluated by interested study groups for reproducibility and/or results of prognostic value.

REFERENCE

1. KREYBERG L. Histologic Typing of Lung Tumours. Geneva, World Health Organization, 1967.

PANEL REPORT

Diagnosis, Staging, and Criteria of Response to Therapy for Lung Cancer

David T. Carr [1,2]

Two panels were devoted to certain aspects of the diagnosis of lung cancer, the staging of the anatomic extent of the cancer, and the criteria for the measurement of the response to the treatment of the cancer. This report summarizes the general opinions of the participants in these two sessions, calling attention to current knowledge and opinion and pointing out areas where critical research is needed.

Diagnosis

Classification by Cell Type

There was essentially unanimous agreement that lung cancer is not a single disease but is a group of malignant diseases and that all cases of lung cancer should be classified by their predominant cell type. Furthermore, all lung cancer reports should group the cases by cell type and analyze the groups separately.

Accuracy of Cytologic Studies of Secretions

There was general agreement that the examination of stained smears of various body fluids is an accurate procedure in the diagnosis of lung cancer. This procedure results in very few false positive reports, and the cytologist can determine the cell type of the cancer in a high percentage of cases.

Occult Carcinoma

A discussion of the problem of sputum-positive/X-ray-negative cases revealed that thorough study of such patients using the fiberbronchoscope and other new diagnostic techniques for localization of carcinoma in situ and small early invasive carcinomas is mandatory. When this is done, most so-called occult lesions can be localized and probably resected, resulting in a very gratifying 5-year survival rate.

Mediastinoscopy

Most participants agreed that mediastinoscopy is a safe diagnostic examination used to obtain histologic proof of cancer in some patients and to determine the presence of cancer in the mediastinal nodes in other patients already proved to have lung cancer. In at least some cases, this procedure prevents an unnecessary diagnostic thoracotomy and in others a futile exploratory thoracotomy that merely determines the unresectability of the cancer. It should be pointed out, however, that there was not agreement that mediastinal nodal involvement contraindicates an attempt at curative resection, particularly if the nodes involved are subcarinal or ipsilateral paratracheal nodes adjacent to the distal half of the trachea.

Scalene Node Biopsy

In contrast, it was agreed that in the absence of palpable scalene or supraclavicular nodes, the "blind" biopsy of these nodes is not worthwhile.

Detection of Osseous Metastasis

Osseous metastasis may or may not cause symptoms. The diagnostic study of patients with symptoms is not a great problem; however, the detection of asymptomatic osseous metastasis is not only a problem but is of great importance.

Evidence was presented proving that routine

[1] Division of Thoracic Disease and Internal Medicine, Mayo Clinic, Rochester, Minn.

[2] I wish to thank the many participants who presented their data, the discussors, the staff who made so many special arrangements on such short notice, and especially Dr. Aron Primack who assisted in the preparation of this summary report. I take full responsibility for the accuracy of this report and apologize for any errors or misquotations.

bone marrow biopsy is advisable in all small cell cancers to determine the extent of the disease. Further research is needed to determine the value of this examination in the other cell types.

Although little data was presented, it was agreed that a roentgenographic bone survey or a radioisotopic bone scan, preferably the latter, is advised in all cases.

Detection of Hepatic Metastasis

Hepatic metastasis is common and difficult to diagnose when the lesions are few and small. It was agreed that it is practically impossible to prove the absence of hepatic metastasis. All patients with lung cancer should have a battery of liver function tests and a careful physical examination to detect hepatomegaly. If there is any abnormality, a radioisotopic liver scan is advisable. If the results of this test are abnormal, a needle biopsy should be done to determine the cause of the abnormality. Unless metastatic cancer can be demonstrated, the patient should be treated as though hepatic metastasis had been excluded and the liver should be observed carefully for subsequent developments. Peritoneoscopy for evaluation of the liver is still undergoing research, and it was agreed that diagnostic laparotomy is not advisable.

Detection of Intracranial Metastasis

It was agreed that no routine examination is available at this time for the detection of asymptomatic metastasis to the brain. However, it was suggested that in the near future radioisotopic scanning techniques might make possible total body scanning for metastasis anywhere in the body. In relation to this and all other new diagnostic tests, it was emphasized that new diagnostic tests should be subjected to the same critical evaluation that is required for experimental therapy of lung cancer.

Staging

TNM Classification System

There was general agreement that the anatomic extent of each patient's cancer should be determined at the time of diagnosis and described by a TNM system. There was not unanimous acceptance of any specific TNM system but the differences in various systems are not great.

Grouping of various TNM combinations into stages did not seem to be of great importance. It was pointed out that a TNM classification could be established for a patient after a complete diagnostic workup but prior to a thoracotomy. The surgeon's report could be used to establish a more accurate TNM classification and an even more accurate classification could be created after the pathologist has examined the resected specimen.

It seems inevitable that several TNM systems will be used in the next few years so a plea was made that all published reports of lung cancer give the details of the TNM system used to classify the cases described in the report.

Other Classifications

In addition to cell type and anatomic extent, mention was made of other characteristics of the cancer and the host that might be of importance. Those related to the cancer were (*a*) grade of malignancy, (*b*) cell doubling time, and (*c*) presence of vascular invasion. Host factors were (*a*) performance index, (*b*) symptoms due to the cancer, (*c*) weight loss, (*d*) psychologic index, (*e*) age, (*f*) sex, (*g*) race, (*h*) occupation, (*i*) smoking history, and (*j*) concomitant diseases.

Criteria for Evaluation of Response to Therapy

Survival Rates

The survival rate is the most objective criterion available. However, it can be calculated in various ways, and the exact method that is used should be given in each presentation of survival data.

Regression of Lesions

The importance of this criterion was emphasized repeatedly. The exact method of determining regression of measurable and unmeasurable lesions was not always specified. There is need for a generally acceptable routine method, and utilization of that method should be mentioned in all reports.

Performance Status

There is also need for a standard perform-

ance index since a change in the patient's ability to carry on with his life is a very important criterion for the evaluation of the results of therapy. This index measures quality in the same way that the survival curve measures quantity. Also needed is some method of adjusting the performance index to correct for the impact of concomitant diseases. Related to the performance index is the relief of certain symptoms and signs of the cancer such as pain, cough, hemoptysis, dyspnea, dysphagia, superior vena caval obstruction, obstructive pneumonitis, and pleural effusion.

Body Weight

Unexplained decrease in body weight is a frequent sign of progressive cancer even when no progressive malignant lesion can be seen.

Blood Tests

Blood tests that measure certain constituents in the blood and the function of certain organs such as the liver are useful criteria. Special mention should be made of measurements of antitumor antigens, measurements of certain hormones (such as the antidiuretic hormone) secreted by certain tumors, and electromyograms in patients with the myasthenic syndrome.

Future Prospects

Possibilities for the future include serial studies with the fiberbronchoscope and serial biopsies or fine-needle aspirations combined with cell kinetic studies, electron microscopic examinations, and special histochemical studies.

PANEL REPORT

The Surgeon's Viewpoint on Collaborative Research on Lung Cancer

Clifton F. Mountain [1]

SUMMARY

The results of surgery in treatment of lung cancer patients are remarkably uniform while surgery continues as the therapeutic modality offering the greatest promise for long-term survival. It has, for the most part, reached its zenith of development. Meaningful improvement in the survival of patients treated surgically can only be realized through the application of effective adjunctive therapy. Accurate assessment of the initial total tumor burden and measurement of the "disease-free interval" are important unsolved problems. The therapeutic role of surgery can be identified for various subsets of the population of lung cancer patients classified by the anatomic extent of disease.

[Cancer Chemother Rep Part 3, vol 4:307–309, 1973]

I wish to express my sincere appreciation to the members of the Surgery Panel, both for their individual contributions and for their collective spirit in this week's enterprise. The discussions were particularly profitable, and debate, with the expression of different viewpoints, was in no way counterproductive. I believe it fair to say that there was remarkably little divergence of opinion concerning the important central concepts of our collective thinking.

The development of thoracic surgery in the therapy for lung cancer was reviewed for historical perspective. The end-results of surgical therapy, both in the United States and abroad, were presented. The following points were confirmed:

1. The results of surgical resection of lung cancer are remarkably uniform throughout the world. The current mortality rate from surgical resection is between 5% and 10%.

2. Surgeons no longer consider undifferentiated small cell (oat cell) carcinoma as a surgical lesion. With few exceptions, resections are not knowingly undertaken in this disease. There is the special case, however, of a coin lesion which is resected for diagnosis. Although these lesions constitute a very small subset of the population, in the absence of any lymph node involvement or blood-borne metastases some 5-year survivors may be seen. It cannot, therefore, be said with certainty that coin lesions known to be oat cell carcinoma should not be resected. The studies of the Veterans' Administration should prove very helpful in establishing this point, and we must keep an open mind.

3. Surgeons have great confidence in their craft and retain the conviction that resection continues to be the only promising route to survival. They are unequivocal in their accord that any stage I or II squamous cell carcinoma, adenocarcinoma, or undifferentiated large cell carcinoma should be resected. The percentage of patients in these categories surviving 5 years

[1] Thoracic Surgical Service, Department of Surgery, The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston.

will range from 50% to 12%. There is less unanimity of opinion regarding the advisability of resecting tumors when the mediastinal lymph nodes are involved. It is appreciated that, without consideration of any other factor, the 5-year survival rate in patients with mediastinal lymph node involvement is no more than 3% regardless of cell type. The surgical survival rate, however, is materially improved if one considers the patients with squamous cell carcinoma in which only the low ipsilateral and/or subcarinal lymph nodes are involved, ie, $N_{2.1}$ lesions. Only a few surgeons will operate with the knowledge that a high ipsilateral mediastinal node is involved ($N_{2.2}$), and then only when such nodes are solitary and their capsules remain intact.

4. The indications for palliative resection are definitely limited. Some feel very strongly that there are *no* indications when one views the ratio between survival and operative mortality in such cases.

5. Very importantly, there is general acceptance of the concept that lung cancer is a systemic disease at diagnosis in a majority of cases. It is agreed that therapies adjunctive to surgery must be actively investigated. Any material or truly meaningful improvement in survival will only be realized if effective adjuncts are employed. This excludes the unlikely possibility that some new therapy will be discovered which is, in itself, curative. This is to say that the contributions of surgery, with respect to their influence on survival, cannot be expected to change. We believe in the concept of biologic operability as opposed to technical resectability. Surgery has essentially reached its anatomic extent and it is felt that the future lies with chemotherapy, immunotherapy, and radiation therapy.

The panel reviewed the progress in chemotherapy with respect to new agents and adjunctive trials. It was generally agreed that no clearcut advantages could be seen in current investigations where strictly randomized protocols had been followed.

The subject of testing for immunocompetence was reviewed. It is clear that most surgeons are not currently acquainted with the new terms and concepts of their colleagues with expertise in immunology. Surgeons will have to do more homework with respect to this subject. Yet, there is clearly a great interest in the concepts expressed and, I believe, a sensitivity to the potential for meaningful developments. There is particular interest in the clinical demonstration of the very high negative correlation between the demonstration of tumor non-specific immunocompetence and metastases in lung cancer. I believe surgeons will be willing and ready to utilize applicable developments in immunology as soon as preliminary studies can be confirmed.

The discussion of preoperative diagnostic and evaluative studies was most provocative. It is felt that diagnosis prior to thoracotomy should be possible in 90% of patients. For investigational studies, objective assessment of the mediastinum, by either mediastinoscopy or mediastinotomy, is deemed advisable. Studies were reported which compared the extent of disease by clinical estimation with that established by autopsy in patients dying within 30 days of "curative surgery." In one half of the patients there was clear evidence of metastatic spread of disease. In many instances more than one organ was involved. It is agreed that one of the single most important problems that we face is our inability to correctly assess the true anatomic extent of disease, ie, the accurate evaluation of total tumor burden.

Obviously some reliable system of "markers" is desperately needed to reliably and validly identify the presence of metastases. Their relationship to altered metabolic states, to the immune status, and to carcinoembryonic antigen was discussed. The measurement of fibrinogen, calcium, and parathyroid hormone was suggested. The provocative question was raised: "Should we not operate on patients with anergy?"

Apropos to this discussion, and therefore of great interest, was the presentation of preliminary work on radioactive tracers. The tagging of bleomycin (NSC-125066) with cobalt 55 is an example of a double potential in that it measures both the tumor site and the distribution of the drug. Metabolic pathways may also be further elucidated. Mercury 197 was shown

to localize and demonstrate metastases in mediastinal lymph nodes.

The Panel specifically addressed itself to the problem of superior sulcus tumors as a special case. It was agreed that in this disease there is wide variation in end-result reports of the efficacy of preoperative irradiation. The Panel also felt that careful definitions of these lesions are important; namely, that a distinction should be made between a superior sulcus tumor associated with a true "Pancoast's syndrome" and one associated with a "painful apical syndrome." The latter group could be expected to have a superior prognosis. It is felt that the best methods for managing this tumor remain to be conclusively proven and that the role of definitive radiotherapy needs to be clarified. The necessity of objectively proving the histologic presence of malignancy prior to initiating therapy was stressed.

A report of recommendations from the Committee on Surgery of the Working Party on the Therapy of Lung Cancer was distributed to the Panel but was not discussed in its entirety. No marked disagreement with its contents has come to my attention, but this may simply reflect the polite and gentle behavior of the conferees. In any event, the report remains open to constructive criticism.

In summary, surgeons strongly subscribe to the concepts of reductive surgery and the principle of adjunctive therapy. They want to see emphasis placed on the development of better tools for the assessment of tumor burden. They subscribe to (*a*) the essential value of objective proof of disease prior to initiating therapy; (*b*) the values of clinical staging; and (*c*) the need for stratification of disease by cell type for purposes of end-result reporting and for planning therapeutic trials. They can identify the role of surgery in terms of the clinical classification detailing the anatomic extent of disease, and they propose that new investigational therapeutic strategies be developed for the various subsets in the population of lung cancer.

"Medicine is like sailing—part art, part science. When man first gained an understanding of sails and harnessed the power of the wind, he extended his limits of travel and measurably increased his capacity for collecting knowledge. In so doing he learned more about the very power that was moving him." Continued research into the perplexing problems of lung cancer will similarly never be in vain.

PANEL REPORT

Radiotherapy for Lung Cancer

Philip Rubin [1]

SCOPE OF PROBLEM

The rising incidence of lung cancer makes this cancer the number one killer among neoplasms. It is predicted that 75,000 new cases are diagnosed each year in the United States. With careful selection, 25% of these patients will be surviving 5 years after surgical resection using current methods of treatment. The disease is lethal, however, in 90%–95% of the diagnosed cases. The number of patients submitted to surgery has been reduced because histopathologic diagnosis is now possible through the use of brush biopsy and needle biopsy under fluoroscopic control and through the use of newer methods of washout cytology with fiberoptic bronchoscopes. Thus, 85% of the patients can be diagnosed before definitive treatment is attempted. Lung cancer is considered beyond the scope of surgical resection in 85% of all cases by the time of initial diagnosis.

THE CHALLENGE

With the acknowledgement of the high level of lethality of lung cancer, it is important to recognize the need for careful investigation. There is a reluctance to engage in clinical trials since most of the available modalities are largely ineffective in leading to survival. Nevertheless, the admission by the surgical, radiologic, and medical community that "we cannot do worse" demands a two-phase attack on the problem and the establishment of a priority system for clinical trials. The first phase is a critical assessment of the value of current standard treatment(s) in lung cancer and of combinations advocated in the literature. The second phase is to identify as rapidly as possible potential new leads in chemotherapy and new modes of immunotherapeutic treatment to be used with the best standard radiation and surgical treatments. It is essential to define the effectiveness of radiation therapy.

The ability of radiation therapy to produce local tumor ablation and nodal sterilization has been documented by a study of surgical specimens after completion of a preoperative course of irradiation and by the analysis of postmortem lung specimens submitted to definitive irradiation. However, there is little evidence that clinical results as measured by long-term survival rates have been improved by the use of irradiation in unresectable disease or by combined irradiation and surgery in resectable regional disease. The major issue is to define the *most effective* radiation therapy scheme to provide a basis for combination of irradiation and other modalities to achieve control of tumor and nodal involvement in both regionally resectable disease and unresectable disease. This implies a standard daily dose and fractional number per week. The definition of effective therapy in this context is maximal tumor control with minimal complications in vital normal tissues exposed to irradiation. This will yield the maximal total dose that will be tolerated and will be related to the volume of irradiated lung and mediastinum.

With the identification of the most effective treatment dose, there is a need to establish the *most efficient* treatment schedule. The definition of efficiency implies effective dose delivery in a minimal period of time and the optimal fractionation or split dose schedule to achieve tumor ablation or tumor control. This may lead to revision of the recommended total dose. With

[1] Division of Therapeutic Radiology, The University of Rochester School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, NY.

the establishment of the most effective and most efficient dose schedule, a basis for the combination of irradiation with surgery, chemotherapy, or immunotherapy will evolve.

BASIC OBJECTIVES OF RADIATION THERAPY STUDIES IN LUNG CANCER

A cooperative clinical trial is an ideal means to achieve the following goals:

- Determine the most effective and efficient radiation therapy regimen which will control primary bronchogenic carcinoma and metastasis in regional nodes (T and N control).
- Ascertain the value of radiation therapy to specific target groups defined by anatomic extent (stage) and histopathologic type as measured by quantity and quality of survival.
- Define dose-response curves for local tumor control versus complications in normal pulmonary tissues.
- Determine the optimal fractionation schedule for bronchogenic carcinoma comparing continuous and split-course schedules.
- Establish the effectiveness of surgery in combination with radiation therapy given either preoperatively or postoperatively versus either modality alone.
- Determine if prophylactic irradiation to extended fields covering potential regional nodal spread is superior to treatment of involved nodes only.
- Determine if prophylactic irradiation to distant visceral areas of spread such as brain and liver is worthwhile.
- Determine if adjuvant chemotherapy in combination with radiation therapy and/or surgery can offer an increase in tumor control and survival.
- Accumulate material which when adequately analyzed will provide accurate information regarding the natural history and biologic characteristics of cancer of the lung as well as the mechanisms of failure for the various methods of treatment.
- Design multidisciplinary studies to set the stage for future protocols combining irradiation with multidrug chemotherapy and/or immunotherapy.

PLAN OF ACTION

A Unified Classification

It is considered essential that a mutually agreeable classification be adopted for definition of target groups and end-stage reporting. The classification offered by the Surgical Committee of the Working Party on Lung Cancer is commendable but essentially takes a surgical view of the disease. It fails to distinguish the two subcategories of those patients who receive irradiation: those with lesions in which long-term local control or sterilization is feasible and those with lesions that are beyond local control and in which palliation is the only objective of irradiation. The designation of an all-encompassing group (T3) subdivided by decimals, as recommended by the Surgical Committee, does not meet the demands required of protocol design in radiation therapy and eventual combination chemotherapy. The T3 category as listed by the Surgical Committee should be modified by division into T3 and T4 categories:

T3 (Extrapulmonary limited and intrathoracic): This group includes primary lesions which invade through the visceral pleura and are adherent to the parietal pleura. Localized bronchogenic cancers within 2 cm of the carina are essentially extrapulmonary. There is no evidence of visceral, vascular, neurologic, osseous, or cardiac (including pericardial) invasion.

T3.1: Primary lesion meeting above criteria and limited to one lobe including associated atelectasis and infiltration.

T3.2: Primary lesion meeting above criteria and limited to two lobes.

T3.3: Primary lesion meeting above criteria and limited to one main bronchus without atelectasis.

T3.4: Primary lesion meeting above criteria with associated pleural effusion with negative cytology, indicating extensive mediastinal adenopathy and venous compression. This type of lesion is modified by virtue of nodal involvement and is not necessarily an advanced lesion.

It is important to recognize that thoracic exploration may be required to identify T3 lesions. Such categories as T3.1, T3.2, and T3.3 represent T1, T2, and T3 lesions clinically and radiographically assessed, which are beyond resection due to location or evidence of extrapulmonary invasion uncovered at the time of surgery.

T4 (Extrapulmonary and/or extrathoracic): This group includes very extensive primary lesions invading into the nerves, major vessels, and cardiac

and osseous sites. They are beyond the parietal pleura and are in the chest wall, viscera, and deep mediastinal structures.

T4.1: Associated with total collapse of involved lung with any primary lesion.

T4.2: Positive pleural effusion cytology with any primary lesion.

T4.3: Superior vena caval obstruction with any primary lesion.

The nodal categories, as currently listed, need further classification of all intrathoracic groups. As stated, they are acceptable with the following modifications:

N0: No demonstrable spread to lymph nodes.

N1: Ipsilateral hilar nodes.

N2.1: Subcarinal (ipsilateral) and lower mediastinal (ipsilateral) involvement.

N2.2: High mediastinal involvement.

N2.3: Contralateral, hilar, and mediastinal nodes.

N2.4: Posterior mediastinal nodes and diaphragmatic and pericardial involvement.

N3: Supraclavicular nodes and scalene nodes.

All other nodes which are extrathoracic and palpable are placed into metastatic (M) disease categories (cervical, axillary, or abdominal celiac nodes). Subcarinal nodes which spread the carinal angle are beyond resection. The designation of ipsilateral is warranted to meet the N2.1 category. There is little distinction between high mediastinal and scalene node biopsies; therefore, grouping both into N2.2 is reasonable. Contralateral nodes are classified as N2.3 and retrograde flow into lower mediastinum is listed as N2.4.

M (Distant metastasis):

M1: Solitary, isolated metastasis confined to one organ or one anatomic site.

M2: Multiple metastatic foci confined to one organ system or one anatomic site (ie, lungs, skeleton, liver, etc) resulting in minimal or no functional impairment.

M3: Multiple organs involved anatomically resulting in minimal to moderate or no functional impairment.

M4: Multiple organs involved anatomically resulting in moderate to severe functional impairment.

The need to define target groups with clarity and precision is essential to protocol development and rests upon distinction in the tumor and nodal categories as outlined. The stage grouping is of less importance in developing target groups.

Standardized Workup

There is agreement that we need a standard workup and a statement regarding mandatory and optimal investigative procedures. The principle of clinical-radiographic staging versus surgical-pathologic staging for tumor extent should be carefully documented, ie, T and N designated with subscripts (s = surgical exploration and + = pathologic assessment).

The following pretherapy studies are indicated:

(*a*) Chest films: postero-anterior and lateral views;

(*b*) Bronchoscopy and biopsy;

(*c*) Sputum cytology × 3 (if positive biopsy is not available);

(*d*) Complete blood cell count including wbc, differential, and platelets;

(*e*) Blood chemistry profile including liver function studies (SGOT, SGPT, LDH, bilirubin, alkaline phosphatase, and serum creatinine);

(*f*) Pulmonary function studies;

(*g*) Chest tomograms for hilar located disease (indicated for all histologies, the exception is the well-differentiated epidermoid cancer);

(*h*) Bone marrow biopsy or core in oat cell cancer.

The following studies are optional but highly desirable:

(*i*) Skeletal, brain, and liver scans;

(*j*) Skeletal survey if symptomatic or bony lesions are suspected;

(*k*) Mediastinoscopy;

(*l*) Bone marrow scan;

(*m*) Immunologic competence, ie, skin testing to a battery of antigens.

Other less critical optional studies include:

(*n*) Bronchograms.

Patterns of Failure

Patterns of failure should be carefully documented with the same indices developed for pretreatment. A TNM recurrence classifica-

tion with careful geographic mapping of tumor, rather than reports on survival alone, is critical. This could be done by placing the letter R (for recurrence) before the T and N category which can be the same as the advocated pretreatment categories. The host complications secondary to the disease or treatment need to be carefully recorded. Maintaining contact in terminal phases as well as during hospitalization is essential to provide the best care and to be in a position to perform careful postmortem examinations. The exact mechanism(s) of failure and disease persistence or spread particularly in tumor and nodal compartments in relationship to disease encompassed by surgery and/or irradiation must be determined to develop new treatment strategies.

If primary and regional nodal disease can be controlled by irradiation and/or surgery, chemotherapy can be utilized for ablating distant microfoci or occult metastases. If the tumor and nodal compartments are not controlled, chemotherapeutic agents will be required to augment the effectiveness of irradiation either by radiosensitization and enhancement or by addition through its own action.

The radiation treatment of occult metastasis is worth consideration in such specific high-risk organ sites as the brain. Doses required to obtain eradication of occult metastases are within tolerance and may be effective where chemotherapeutic agents are unlikely to be of value.

Establishment of Conversion Ratios

The ability to eradicate tumor and nodal disease in different target groups allows for identification of the incidence of occult metastases at the time of initial therapy. This assumes that the local therapy administered is effective locally and regionally and that the development of metastases is due to undetected deposits present at the time of initial diagnosis.

New Strategies

With the establishment of failure pathways and conversion ratios, new combinations of existing modalities will follow. Sequences of standard treatment can be altered and utilized concurrently. The place of immunotherapy will be more logically developed, particularly in patients with low risk of metastasis, where nonspecific stimulation may be more effective since intact immunocompetence exists. The evaluative procedures to determine tumor response will require a better understanding of tumor biology since regression and disappearance patterns of tumors are of limited predictive value. Similarly, prediction of radiation complications is not possible by present methods and deserves more study.

RESEARCH ALTERNATIVES AND PRIORITIES

The future alternatives and priorities include answering questions concerning radiation therapy which are raised in uncontrolled studies but unanswered in the literature.

a. What is the best treatment schedule for lung cancers?

b. Is postoperative irradiation of value for microdeposits in lymph nodes?

c. Is preoperative irradiation of value in apical tumors?

d. What is the most effective and efficient schedule for combination chemotherapy and radiotherapy?

e. What are the dose-response curves for local tumor control and complication in pulmonary tissues?

It will be our task to develop innovative approaches to the effective radiation treatment of lung cancer. These approaches include:

a. Assessing the value of elective irradiation to visceral sites for occult metastases such as brain, liver, and kidneys.

b. Determining if combination adjuvant chemotherapy and radiation therapy can control occult metastases.

c. Seeking radiosensitizers to reduce the effective radiation dose for local tumor control.

d. Determining the effect of lung cancer and radiation therapy on immune responses by pretreatment and posttreatment skin tests.

e. Defining a group of patients in which BCG (Bacillus Calmette-Guérin) stimulation could be attempted to assess the benefits of nonspecific stimulation.

In conclusion, the design of protocols should be to provide "total therapy" to all compartments of disease: local tumor, regional nodes, and distant metastases. Rather than a competitive approach as utilized in the past, each modality should be utilized as a reductive procedure of the tumor burden. As each treatment is combined effectively and efficiently in a logical sequence before the overt appearance of metastases occurs, increased tumor control and survival of this dreaded cancer may eventuate.

PANEL REPORT

Interdisciplinary Group on Clinical Trials (Biostatistics)

Marvin Zelen [1]

Although this panel was originally intended to be a biostatistics panel, it was in truth interdisciplinary in scope. Hence, I have taken the liberty of changing the name to *Interdisciplinary Group on Clinical Trials*. Perhaps it was one of the few interdisciplinary panels at this Workshop. In my experience, it has been one of the most stimulating panels I have participated in, and I would like to thank all the participants for making it so interesting and useful.

During the course of our meetings we discussed many methodologic problems arising in recently conducted clinical trials of bronchogenic carcinoma and the possible approaches to be used in conducting future trials. Due to a conflicting schedule with the Radiotherapy Panel, our Panel suffered from lack of more active participation by the radiotherapists, and, as a result, topics associated with radiotherapy were not discussed at any great length. This is reflected in our position recommendations which deal mainly with chemotherapy and its role in clinical experimentation in lung cancer.

The sessions were conducted so that the formal presentations were short. This allowed a great deal of time for discussion. Before presenting the Panel's recommendations, I would like to discuss briefly some of the topics discussed.

1. *The credibility of clinical trials.*—Clinical trials must be conducted in such a way that other investigators will accept the results. This means that the study population must be clearly defined; the differences between the study population and other target populations must be outlined; and sweeping conclusions based on small sets of data must be avoided.

2. *Integrity of data.*—We must be careful, especially in multi-clinic trials, that there is effective quality control of the data. A trial is only as credible as its weakest institution. An institution which continually violates protocols, is late in reporting, and reports fragmentary information can destroy the credibility of the trial. We must restrain ourselves from attempts to collect large amounts of secondary information which are likely to discourage all but the most dedicated of investigators.

3. *End-points in a study.*—Care must be taken in considering how the various endpoints in a study are judged. Survival is not as clearcut a response variable as many people believe, especially in advanced disease. Because survival can be considerably affected by supportive therapy, minimum supportive therapy should be carefully delineated in any protocol.

4. *Natural history of disease.*—The Panel had much discussion on using the natural history of bronchogenic carcinoma in planning prospective trials. All the panelists agreed that the important features of the natural history of the disease should be employed in planning trials. This also includes appropriate stratification for allocating patients to therapies.

It was very clear in our discussion that a proper evaluation of the results from clinical trials must take into account all important known factors which are likely to affect the outcome. There are a large number of such factors, ie, histology, performance status, prior therapy, thoracic and extrathoracic signs and symptoms, time from initial diagnosis, anatomic staging, etc.

We discussed the possibility of organizing a data bank of bronchogenic cancer patients which could be used for making adjustments of prospective trials with regard to many of these factors. A data bank, used in conjunction with

[1] State University of New York at Buffalo.

more sophisticated statistical methods, may help overcome the problem of how to adequately evaluate a prospective clinical trial with a modest number of patients.

POSITION RECOMMENDATIONS

The possible broad areas of patient classification for prospective clinical trials of chemotherapy in bronchogenic carcinoma are:

1. Extensive disease
2. Limited disease: inoperable, primary treatment is radiotherapy
3. Operable disease: noncurative
4. Operable disease: curative

Much of the clinical effort in chemotherapy is in category 1, extensive disease. In our discussions it quickly became apparent that results from different institutions and cooperative groups on similar agents are not comparable. This is mainly due to the lack of precise definitions for the patient population, the variability of the natural history of the disease, and the different criteria of response. The Panel felt very strongly that it will be difficult to make progress until we are able to compare results from different institutions, different cooperative groups, and different countries. Due to the urgent need for comparability, we strongly propose the following recommendation for extensive disease clinical trials.

Recommendation 1: Concomitant Control

All future phase II clinical trials on a new agent are to be conducted so that the new agent is compared in a prospective randomized trial using cyclophosphamide as a concomitant control.[2] The dose recommended is 1.1 g/m² every 3 weeks with an escalation schedule if minimum toxicity is observed. No prospective trials will be conducted using patients with a Karnofsky performance scale rating less than 40 (disabled; requires special care and assistance).

This is our principal recommendation. Personally, I regard it as the most important recommendation resulting from this International Workshop. Full credit should be given to Dr. Kenis, who suggested it. We spent several days listening to many clinical presentations, and it is obvious that the results from these studies are not totally comparable. Real progress will not be made until there is a way of comparing results from different institutions and cooperative groups. Others thought it was such a good idea that it evidentally surfaced in other Panels after being adopted by our Panel.

[2] Cyclophosphamide: NSC-26271; CAS reg. No. 6055-19-2; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)-amino]tetrahydro-, 2-oxide, monohydrate.

Recommendation 2: Strategy In Experimentation

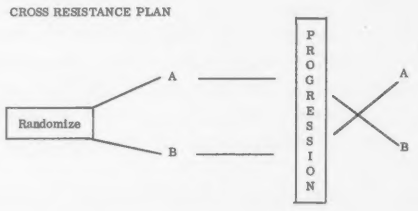
In order to make progress in treating bronchogenic carcinoma we must adopt a clear strategy in our overall scientific effort. As a minimum, we recommend the following strategies.

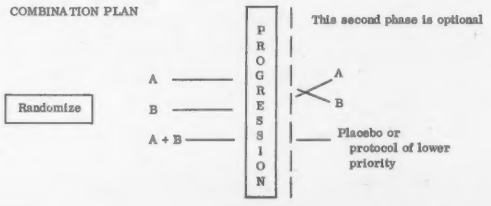
If a phase II trial results in an agent being declared "statistically effective," it is strongly urged that further followup trials be conducted to investigate: (a) cross resistance of the new agent with other agents believed to be effective; (b) comparison of the single agent with a combination which includes that agent.

Investigating how the promising new agent behaves with other agents is suggested because past experience in several cancer sites has indicated that combination chemotherapy is significantly more effective than single agent chemotherapy.

Recommendation 3: Simple Experimental Plans

The Panel further recommends that the two experimental plans (shown below) be used for investigating cross resistance and combination therapy.





The second phase of the combination plan is optional and is a possible way of relating the cross-resistance plan to the combination plan.

Recommendation 4: Guidelines for Selecting Patients in Earlier Disease Stages

It has long been felt that the beneficial effects of chemotherapy may be substantially enhanced if patients with earlier disease are used in clinical trials. The following recommendation lists guidelines to be followed in selecting earlier disease patients for study.

A. There must be a statistically demonstrated objective response with acceptable toxicity in patients with extensive disease before the agent is used in trials of limited disease (inoperable).

B. There must be at least a 20% statistically demonstrated objective response with acceptable toxicity in patients with limited disease (inoperable) before the agent is used in trials of operable cases (noncurative).

C. There must be at least a 10% statistically demonstrated objective response with acceptable toxicity in operable cases (noncurative) before the agent is used in trials of operable cases (curative).

Recommendation 5: Coordination

Our final recommendation deals with coordination. At the present time there are only a small number of promising chemotherapeutic agents used for bronchogenic carcinoma. Any new agent having moderately promising initial results is likely to be investigated in several cooperative groups and institutions. To avoid needless duplication, the Panel makes the following recommendation.

It is strongly urged that cooperative groups or institutions conducting prospective clinical trials on the same agent develop a mechanism for coordinating their efforts to avoid needless duplication.

In closing, I hope that the recommendations put forth by our Panel will receive serious consideration by the community of investigators interested in bronchogenic carcinoma.

ANNOUNCEMENT

Medical Oncology Course

Presented by The University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute at Houston in cooperation with The University of Texas Health Science Center at Houston Division of Continuing Education
September 24–28, 1973

This comprehensive, intensive course is designed to review current concepts of the natural history, diagnosis, therapy, and clinical management of the spectrum of malignant disease cared for by the medical oncologist. In addition, brief reviews will be given of the current status of viral oncology and tumor immunology. The course will consist of 32 hours of didactic lectures with time for discussion. It is scheduled from Monday through Friday, September 24–28, 1973, in Houston. Tuition fee: $150.00

For further information write: The Office of the Director, The University of Texas Health Science Center at Houston, Division of Continuing Education, P.O. Box 20367, Houston, Tex 77025.

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